EMOTIONAL WORKING MEMORY:

THE ROLE OF DEVELOPMENT AND TASK FACTORS

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Emotional working memory:

the role of development and task factors

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Sofie

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CHAPTER 1

GENERAL INTRODUCTION

"Sometimes the heart knows things the mind can never explain."

Ranjit Singh

Throughout history, emotion and cognition have traditionally been considered as two opposing forces: head versus heart, reasoning versus intuition, and thinking versus feeling. For a long time, this opposition has guided psychological research to study both functions as separate independent processes. However, to understand complex and dynamic human behaviour, it is necessary to examine the interplay between both, since our actions and decisions can never be considered purely cognitive or purely emotional. Instead, they influence each other and the resulting behaviour is always a combination of both.

Recently, there has been an increasing interest in the reciprocal interactions between emotional and cognitive processes and how these interactions underlie motivated behaviour. One of the reasons behind this shift in focus, from studying emotion and cognition in isolation to investigating their interaction, are advances in cognitive and affective neuroscience. Studies in this domain have shed light on how emotion and cognition are represented neuro-anatomically. In contrast to the prevalent idea of assigning these functions to different brain regions, studies indicate that cognition and emotion are integrated in the brain (Gray, 2004; Pessoa, 2008, 2009). Brain regions that were previously thought to be responsible for cognitive processes, such as the prefrontal cortex (PFC), seem to be sensitive to emotional manipulations (Erk, Kleczar, & Walter, 2007; Goldstein et al., 2007; Perlstein, Elbert, & Stenger, 2002),

and regions traditionally associated with emotional processing are found to be influenced by cognition (Blair et al., 2007; Schaefer et al., 2006; Schaefer & Gray, 2007; Silvert et al., 2007). Therefore, whereas previous research has investigated cognitive processes in an emotionally neutral context or with emotionally neutral information – so called 'cold' cognition – a new research domain has emerged examining how affective information can modulate cognition, i.e. 'hot' cognition. This line of research is concerned with emotional influences on cognitive processes such as attention (e.g. Pourtois, Schettino, & Vuilleumier, 2013; Vuilleumier, 2005), visual processing (Pourtois et al., 2005; Brosch et al., 2008) and cognitive control (Diaz et al., 2011; Dolcos & McCarthy, 2006; Egner, Etkin, Gale, & Hirsch, 2008). Cognitive control is an umbrella term used to describe a variety of mental processes that are required to flexibly adapt behavior to current goals. Examining emotional influences on these processes is thus especially important in understanding goal-directed behaviour.

Miyake et al. (2000) have suggested that cognitive control can be subdivided into three related but separable processes: 1) set shifting, or the ability to switch between multiple tasks or task sets, 2) inhibition, i.e. the ability to voluntarily suppress a prepotent response, and 3) updating, which refers to the ability to maintain and update relevant information in working memory. Although emotion has been found to influence all of these functions (Diaz et al., 2011; Dolcos & McCarthy, 2006; Dreisbach & Goschke, 2004; Egner, Etkin, Gale, & Hirsch, 2008), the latter is thought to play a crucial role in emotion regulation strategies (Joormann & D'Avanzato, 2010; Pe, Raes, & Kuppens, 2013).

Working memory (WM) is a limited-capacity system where information is stored and manipulated over brief periods of time, before transferring it to long term memory (Baddeley, 2003). Given its restricted capacity, controlling which information is actively maintained in WM is crucial to adequately guide our behaviour towards current goals. With regard to affective content, this includes both the ability to keep irrelevant emotional information from entering WM and to effectively maintain and update emotional information if relevant. Previous studies have shown that efficient updating of affective stimuli in WM is related to well-being (Pe, Koval, & Kuppens, 2013) and to personality traits such as optimism and pessimism (Levens & Gotlib, 2012). Furthermore, deficits in (emotional) WM have been found in a range of

psychopathologies, most importantly depression (Joormann & Gotlib, 2008; Levens & Gotlib, 2010; Linden, Jackson, Subramanian, Healy, & Linden, 2011) and anxiety (Fales et al., 2008; Lavric, Rippon, & Gray, 2003; Shackman et al., 2006).

Even though there is an increased interest in WM processes for emotional information in adults, not many studies have examined how this ability develops during adolescence. Nevertheless, adolescents are an especially interesting population in terms of studying the interplay between affective and cognitive processes, since this phase in life is characterized by unique neuropsychological substrates underlying both. More specifically, hypersensitivity to emotional cues in subcortical regions of the brain combined with delayed maturation of prefrontal regions responsible for cognitive control during adolescence is thought to underlie difficulties in emotion regulation abilities (Ernst, Pine, & Hardin, 2006; Somerville & Casey, 2010; Steinberg, 2008). This imbalance is supposed to explain the increase in affective disorders in this developmental period.

In the following sections, we first provide a brief overview of empirical data and theoretical models of emotion-cognition interactions in the adult literature, since these findings can guide developmental research. Second, we focus on adolescence and explain in more detail why this is such an interesting time period to study the integration of affective and cognitive processes. We outline the main propositions of neurobiological theories and discuss available evidence. Third, we focus specifically on findings regarding WM processing of emotional information both in adolescents and adults. Finally, we provide an overview of the different chapters included in this dissertation.

1. EMOTIONAL INFLUENCES ON COGNITIVE CONTROL IN ADULTS

1.1 How does emotion impact behavioural performance on cognitive control tasks?

Since emotion and cognitive control are both broad psychological concepts, the methods that have been used to examine their interaction are quite extensive. Researchers have generally added an emotional dimension to “classic” cognitive control tasks, such as the Flanker task (Hajcak & Foti, 2008; Kanske & Kotz, 2011b), n-back task (Buhle & Wager, 2010; Lavric et al., 2003; Legrain, Crombez, & Mouraux, 2011) or stop-

signal task (De Houwer & Tibboel, 2010; Li, Chao, & Lee, 2009; Padmala & Pessoa, 2010; Verbruggen & De Houwer, 2007). Emotional manipulations include mood induction procedures (Gray, Braver, & Raichle, 2002; Nixon, Liddle, Nixon, & Liotti, 2013; Sommer, Hajak, Dohnel, Meinhardt, & Muller, 2008), the receipt or omission of rewards (Krebs, Boehler, Egner, & Woldorff, 2011; Locke & Braver, 2008; Pochon et al., 2002; van Steenbergen, Band, & Hommel, 2009) and the use of emotional stimuli such as pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999) or faces (Langner et al., 2010; Lundqvist, Flykt, & Ohman, 1998; Tottenham et al., 2009).

Given the variety of paradigms, it is not surprising that the behavioural effects of emotional influences on cognitive control tasks are mixed, with affective content sometimes improving (Kanske & Kotz, 2011a; Levens & Phelps, 2008), and at other times impairing performance (Blair et al., 2007; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos & McCarthy, 2006). A task where emotion has consistently been found to impair performance, is the Emotional Stroop task (Compton et al., 2003; Cothran & Larsen, 2008; Segerstrom, 2001; Wentura, Rothermund, & Bak, 2000). In this adaptation of the classic Stroop paradigm, participants are asked to name the color of an emotion-laden word while ignoring the meaning of that word. In general, slower reaction times have been found for emotional – especially negative – compared to neutral words, known as the emotional Stroop effect. This slowdown is thought to reflect an interference effect of the emotional content of the word, grabbing attention and leading to slower reaction times on the color-naming task. Similar effects have been reported with regard to the emotional go/no-go task. In this task, participants see a range of stimuli and are asked to respond to certain stimuli (go), and to withhold responding to other stimuli (no-go). When emotional stimuli are used, response inhibition is usually reduced (De Houwer & Tibboel, 2010; Hare, Tottenham, Davidson, Glover, & Casey, 2005).

Although emotion has most often been shown to impair performance on a cognitive control task (e.g. Chechko et al., 2012; Compton et al., 2003; Deckersbach et al., 2008; Dolcos et al., 2008; Dolcos, Kragel, Wang, & McCarthy, 2006; Habel et al., 2007; Hart, Green, Casp, & Belger, 2010; Wingenfeld et al., 2009), some studies have found better performance during concurrent affective processing (e.g. Beck, Locke, Savine, Jimura, & Braver, 2010; Erk et al., 2007; Kanske & Kotz, 2011a; Kanske & Kotz,

2011b; Padmala & Pessoa, 2011; Sagaspe, Schwartz, & Vuilleumier, 2011; Schulz et al., 2009). An emotional manipulation that has consistently been found to ameliorate performance on a range of cognitive tasks is reward (e.g. Krebs et al., 2011; Savine & Braver, 2010; Taylor et al., 2004). However, other manipulations have also resulted in enhanced behavioural performance (Albert, Lopez-Martin, & Carretie, 2010; Birk, Dennis, Shin, & Urry, 2011; Erk et al., 2007; Kanske & Kotz, 2011a; Levens & Phelps, 2008). For example, to assess interference of emotional information in WM, Levens and Phelps (2008) administered a recency-probes paradigm. In this task, each trial starts with the presentation of a target list of three words. After a delay of 3s, a probe word is displayed and participants are asked to indicate whether this probe matched a word in the target list. To measure interference, probes could match a word from the target set and/or from the target set in the two preceding trials. Results showed that if the probe was emotional, reaction times were faster, suggesting that emotion enhances interference resolution.

1.2 Dual-competition framework

To explain the inconsistent findings reported in the literature, Pessoa (2009) proposed a dual-competition framework, with emotion affecting both perceptual (bottom-up) and executive (top-down) competition. Emotional stimuli are thought to enhance sensory representations in visual cortex, thus affecting perceptual competition. At the same time, these stimuli will also affect executive control, for example by increasing top-down attention towards the emotion-laden stimuli. The dual-competition framework further assumes that the impact on behaviour will depend on the intensity of affective material. Mildly intense stimuli are thought to enhance processing, leading to better performance, although behavioural effects might be relatively weak. This 'soft' prioritization will occur for both negative (e.g. threatening) and positive stimuli (e.g. reward or erotic stimuli). On the other hand, when emotional content is high in arousal, e.g. stimuli that were previously paired with shock, increased recruitment of effortful control mechanisms will prioritize the processing of this information ('hard' prioritization). However, since these processing resources are shared by other executive functions (i.e. inhibition, shifting, and updating) this will limit the capacity that is available for the cognitive control task, leading to impaired

performance. A recent study by Pessoa, Padmala, Kenzer, and Bauer (2012) tested these assumptions in the context of inhibitory control using the stop-signal task. When stop signals were low in intensity (fearful and happy faces), performance was improved compared to a control condition with neutral faces. However, high-arousing stimuli (previously paired with shock) impaired inhibitory performance.

1.3 The role of task-relevance

Another important factor that might determine the impact of affective content on cognitive control processes is task-relevance. It has been argued that processing of emotion is prioritized (Vuilleumier, 2005) which could, depending on specific task demands, either enhance or impair performance. According to Pessoa (2009), in contexts where emotional stimuli are relevant, their preferential processing will have beneficial effects on performance. However, in contexts where the affective value of stimuli is incidental, performance is impaired due to decreased processing of task-relevant content in favor of processing irrelevant emotional information. Although Pessoa (2009) indicates the importance of task-relevance in determining the impact of emotional content on task performance, this factor was not included in the dual-competition framework, thus limiting its applicability. Furthermore, other researchers have also emphasized task-relevance (Gronau, Cohen, & Ben-Shakhar, 2003; Kanske, 2012; Lichtenstein-Vidne, Henik, & Safadi, 2007, 2012; Okon-Singer, Lichtenstein-Vidne, & Cohen, 2013), although some inconsistency exists with regard to its definition. While some authors define task-relevance as “the stimuli that participants need to process and react to in order to solve the task” (Kanske, 2012, p. 1), others use a broader definition and consider all stimuli that are “in some fashion related to the task in which the subject is engaged” (Gronau et al., 2003, p. 512; Lichtenstein-Vidne et al., 2007, 2012) as task-relevant. In the latter view, even to-be-ignored distractors can be task-relevant if they contain information that is related to the task. For example, in the Stroop task the meaning of the word is considered task-relevant because it refers to a colour, and the task is to name the colour of the word.

Even though the abovementioned definitions differ quite extensively, what they have in common is the assumption that task-relevance refers to the stimuli as a whole, and not to the affective features of emotional stimuli specifically. That is, all of these

theories assume that performance is independent of whether attention is directed to the emotional value of the stimuli. In this thesis, we want to examine how the relevance of the emotional information impacts behavioural performance. In other words, we want to study whether directing attention towards or away from the affective valence influences the impact of this emotional information on behavioural performance and neural activation. This question will be addressed in **Chapters 2, 3 and 4**.

1.4 Neural correlates of emotion-cognition interactions

During the past decade, a wealth of studies has used functional magnetic resonance imaging to investigate the neural underpinnings of emotion-cognition interactions (e.g. Chechko et al., 2012; Chechko et al., 2009; Kellermann et al., 2011; Kouneiher, Charron, & Koechlin, 2009; Lee, Kang, Park, Kim, & An, 2008; Lim, Padmala, & Pessoa, 2008; Van Dillen, Heslenfeld, & Koole, 2009). Despite this increased effort to explore the neural basis of concurrent emotional and cognitive processing, there is still some debate about the regions that are involved and their exact role (Dolcos, Iordan, & Dolcos, 2011; Gray, 2004; Iordan, Dolcos, & Dolcos, 2013; Pessoa, 2008; Pessoa & Adolphs, 2010).

Based on a number of studies in their lab, Dolcos and colleagues have emphasized the interplay between two neural systems, a dorsal system involved in “cold” cognition and a ventral system involved in “hot” cognition (Dolcos et al., 2011; Dolcos & McCarthy, 2006; Iordan et al., 2013). The dorsal executive processing system, which contains the dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC) and posterior parietal cortex, is associated with cognitive control processes, while the ventral affective processing system is thought to be involved in emotional processing and includes the amygdala, ventromedial prefrontal cortex (vmPFC) and ventrolateral prefrontal cortex (vlPFC).

However, this parceled view has been challenged by researchers emphasizing integration between emotion and cognition in several brain regions (Gray, 2004; Pessoa, 2008; Shackman et al., 2011), as opposed to dividing the brain into cognitive and affective regions (Dolcos et al., 2011). For example, Gray et al. (2002) demonstrated that activity in the lateral PFC depended on the emotion that was induced by watching short video clips. While DLPFC activation during a verbal n-back task was increased

when participants were in a negative compared to a positive mood state, activity in this same region showed the reverse effect during a face n-back task, with more activation in the positive compared to the negative mood condition. The selective effect of emotional state on these two tasks suggests true integration of emotion and cognitive control in the lateral PFC. Other proposed integration sites include the anterior midcingulate cortex (Shackman et al., 2011), orbitofrontal cortex, vmPFC, and amygdala (Pessoa, 2008).

Given the lack of consensus on the underlying neurobiological circuitry involved in emotion-cognition interactions, we performed a meta-analysis on fMRI studies reporting emotional influences on cognitive control processes. This study will be discussed in **Chapter 2**.

2. THE IMPACT OF EMOTION ON COGNITIVE CONTROL: A DEVELOPMENTAL PERSPECTIVE

The previous sections provided a brief overview of emotional influences on cognitive control processing in adults, on a behavioural as well as on a neurological level. However, none of the theories that were mentioned includes information on how development might change the way that affective and cognitive processes are integrated. Therefore, in the next sections I will introduce theories about emotion-cognition interactions in adolescence, and discuss research carried out within these frameworks. But first, I will provide some background on adolescent cognitive and emotional development, and how this relates to changes in the brain.

2.1 Adolescence: a time of great potential and risks

Adolescence is an important time period during which a child slowly changes into a mature and responsible adult. It's a time of personal growth during which an identity of the self is formed, new friendships are established and many skills acquired. To allow adolescents to accomplish these goals, a range of biological, cognitive and emotional changes take place. These changes are the underlying mechanisms for the typical behavioural patterns that emerge during adolescence. Even though these behavioural patterns are usually beneficial and allow adolescents to adequately make

the transition to an independent life as an adult, they sometimes have adverse consequences. For example, adolescence is characterized by an increase in risk-taking and sensation-seeking behaviour, resulting in high rates of illegal substance abuse, excessive alcohol intake, unsafe sex and dangerous driving (Dahl, 2004; Eaton et al., 2006; Steinberg, 2008). Another characteristic of adolescent behaviour is their emotional instability and intensity (Barber, Jacobson, Miller, & Petersen, 1998; Larson, Moneta, Richards, & Wilson, 2002; Petersen et al., 1993), which can have deleterious consequences, as reflected in increased suicide rates. Both of these typical adolescent behavioural patterns, i.e. risk-taking and emotional lability, are thought to put adolescents at risk for developing psychopathology. Indeed, studies show that psychiatric disorders such as substance abuse and mood disorders often have their onset in the teenage years, with a peak at age 14 (Paus, Keshavan, & Giedd, 2008). Furthermore, these early-onset disorders are found to be more severe and tend to show higher relapse rates than disorders with an onset later in life (Leverich et al., 2007; Lewinsohn, Allen, Seeley, & Gotlib, 1999). Understanding the mechanisms underlying both typical behaviour in healthy adolescents as well as deviations from normal development is crucial to help reduce its adverse effects.

2.1.1 Cognitive development

Cognitive control, the ability to flexibly adapt behaviour to current goals, continues to develop during adolescence. As a result, adolescents are more and more capable of handling increased demands from their environment. For example, they learn to plan ahead, to think in a more abstract way and to reason about hypothetical situations. Developmental studies have used a variety of experimental tasks (e.g. the Stroop task, Stop-Signal Task and memory span tasks) to investigate the development of cognitive control during childhood and adolescence. These studies have shown linear improvements in cognitive control starting in early childhood and continuing into adolescence and even young adulthood (Giedd et al., 1999; Gogtay et al., 2004), depending on the task that is being used.

As alluded to earlier, at least 3 core processes are thought to underlie cognitive control (Miyake et al., 2000) and research has indicated that these processes show different trajectories throughout childhood and adolescence. For example, Luna,

Garver, Urban, Lazar, and Sweeney (2004) measured performance on an inhibition and WM task in 8-30 year olds. Their results indicated that adult-like performance began at 14 years of age for response inhibition, compared to 19 years of age for WM.

2.1.2 Emotional development

In contrast to the steady, linear improvements in cognitive development mentioned above, advancements in terms of emotional development are less straightforward. Adolescence can be described as an emotionally turbulent period, due to all the physical, social and neurobiological changes that take place during this time. As a result, adolescents have the reputation of being rebellious, oppositional, argumentative, uncommunicative and plagued by mood swings. Indeed, studies measuring daily affect and mood indicate a large variability in emotional states throughout the day (Barber et al., 1998; Larson et al., 2002). Furthermore, adolescence is characterized by an increase in negative affect and decrease in positive affect (Compas, Hinden, & Gerhardt, 1995; Larson et al., 2002; Petersen et al., 1993). These patterns, i.e. emotional instability and increased negative mood, are more evident during early adolescence (10-14 years of age) compared to late adolescence (15-18 years of age). The latter group seems to be able to regulate emotions more efficiently, resulting in a more stable mood (Larson et al., 2002).

Even though most adolescents get through this emotionally challenging time unscathed, some are unable to regulate their emotions adequately, as is evident from the rising prevalence of mood and anxiety disorders starting after puberty (Costello, Egger, & Angold, 2005; Hyde, Mezulis, & Abramson, 2008). Gender differences also arise at this point, with adolescent girls being twice as likely to suffer from depression than adolescent boys (Hyde et al., 2008).

2.1.3 Adolescent brain development

The previous sections clearly show that adolescence is characterized by changes on an emotional and cognitive level, which are related to developmental processes on a neurological level. Our brain develops immensely from birth to late childhood, and during adolescence it is constantly being refined to increase the efficiency with which cortical signals are transported. Structural magnetic resonance imaging (MRI) has

increased our knowledge about changes in grey and white matter volume from infancy to adulthood. While white matter seems to increase linearly from birth until about age 20 (Giedd et al., 1999; Paus et al., 2001; Paus et al., 1999; Pfefferbaum et al., 1994), changes in grey matter are more heterogeneous. Generally, grey matter has been found to increase during childhood followed by a volume loss in adolescence (Giedd et al., 1999; Sowell, Delis, Stiles, & Jernigan, 2001). Interestingly, this decrease in the amount of grey matter differs greatly across brain regions, with somatosensory and visual cortices maturing earlier than regions responsible for more complex functions such as the frontal cortex (Gogtay et al., 2004; Sowell et al., 2003). Two processes are thought to underlie these changes, i.e. myelination and synaptic pruning. Myelination refers to the accumulation of myelin – an insulating layer made up of proteins and lipids – around nerve cells, allowing a quicker transmission of electric signals through the nerves, and resulting in more efficient information processing and communication between brain regions. Synaptic pruning is the process of eliminating weaker synapses and neurons in order to facilitate neuronal transmission through more efficient synaptic connections in the brain. During adolescence, increases in white matter are due to myelination and decreases in grey matter can be explained by a combination of intra-cortical myelination and synaptic pruning (Paus, 2005).

Although structural imaging methods have allowed researchers to map developmental trajectories in the brain, there is no consensus about how these findings relate to behavioural patterns observed during childhood and adolescence. To learn more about brain-behaviour relationships, researchers have used functional magnetic resonance imaging (fMRI). This technique has been used to study a wide range of psychological processes in adolescence, including cognitive (Andrews-Hanna et al., 2011; Blakemore & Choudhury, 2006; Luna, Padmanabhan, & O'Hearn, 2010) and emotional (Monk et al., 2003; Nelson et al., 2003; Yurgelun-Todd, 2007) processes.

Improvements in cognitive control during adolescence are thought to rely mainly on maturational changes in the PFC. As mentioned above, structural studies have shown that this region is the last to mature (Gogtay et al., 2004). Furthermore, fMRI studies have indicated differences in activation between adolescents and adults in prefrontal and parietal cortices while performing cognitive control tasks (Andrews-Hanna et al., 2011; Luna et al., 2010). For example, response inhibition depends on a

widespread network including the inferior frontal gyrus (IFG), DLPFC and premotor areas (Jaeger, 2013; Luna et al., 2010). These regions are differentially activated in adolescents compared to adults when using a variety of inhibition tasks, such as the Go/No-Go task (Rubia et al., 2001; Tamm, Menon, & Reiss, 2002), the Stroop task (Adleman et al., 2002; Marsh et al., 2006) and the Stop Signal Task (Rubia et al., 2001). Similarly, WM relies on a circuit including the vlPFC, dlPFC and medial prefrontal regions (Luna et al., 2010).

2.2 Emotion-cognition interactions in adolescence

2.2.1 Dual-systems models of adolescent behaviour

Although cognitive skills improve linearly during adolescence (Luna, 2009) and underlie important advances in reasoning, planning and decision making, empirical work has shown that these skills are challenged when adolescents are placed in an emotional context. Indeed, research on decision making indicates that in emotionally charged situations, there is a bias towards positive environmental cues, leading to suboptimal and risky decisions (Casey, Getz, & Galvan, 2008; Doremus-Fitzwater, Varlinskaya, & Spear, 2010; Somerville & Casey, 2010). A popular paradigm used to measure the development of affective decision-making abilities is the Iowa Gambling task, since it can be performed by participants in a very wide age range (Crone & van der Molen, 2004; Hooper, Luciana, Conklin, & Yarger, 2004; Prencipe et al., 2011; Smith, Xiao, & Bechara, 2012). In this task, participants are required to choose between four decks of cards that are each associated with differing amounts of monetary reward or punishment. Two of those decks (the 'high-risk' decks) offer big wins, making them quite interesting at first, but since they are also associated with big losses now and then, they result in an overall loss at the end of the task. Although the other two decks (the 'low-risk' decks) yield smaller gains and losses, they eventually result in an overall net gain. Thus, selecting cards from the 'low-risk' decks more often than from the 'high-risk' decks is essential to achieve the task goal, i.e. gaining money. In general, adolescents are found to have a propensity for choosing the 'high-risk' over the 'low-risk' decks more often as compared to both children as well as adults. Furthermore,

Smith et al. (2012) found that this is especially true for early adolescents (ages 10 to 13) in comparison to their younger (8-10 years) and older (14-17 years) peers.

According to dual-systems accounts of adolescent behavior (Casey, Duhoux, & Malter Cohen, 2010; Galvan, 2010; Somerville & Casey, 2010; Somerville, Jones, & Casey, 2010; Steinberg, 2008), this inability to exert sufficient "top-down" control in the context of salient environmental cues can be explained by an imbalance between brain systems related to emotional processing on the one hand and brain systems related to cognitive control on the other hand. While the emotional system is supported by relatively mature subcortical regions such as the amygdala and ventral striatum, the cognitive control system is thought to rely on the still immature PFC (see Figure 1). The main idea of these dual-systems models is that adolescence is characterized by a hypersensitivity to emotional cues that cannot be adequately tuned down by the cognitive control system, given its relative immaturity.

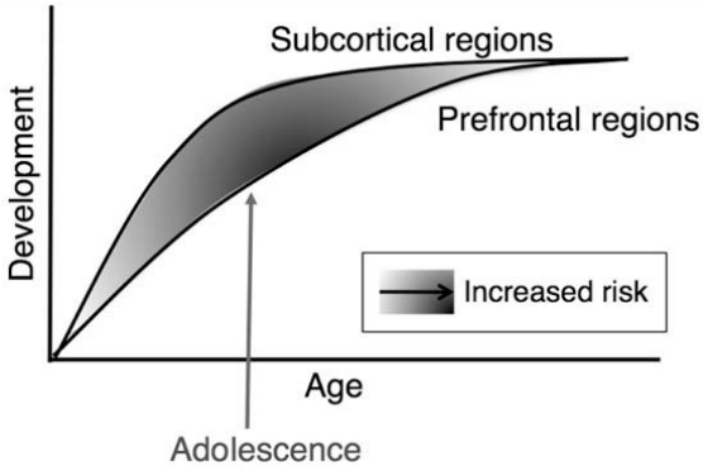

Figure 1. Dual-systems accounts hypothesize that early maturation of subcortical regions, combined with late maturation of prefrontal regions underlie the changes in emotion-laden behaviour in adolescence (taken from Somerville et al., 2010)

Structural neuroimaging work has provided evidence for this protracted development of the PFC in comparison to maturation of subcortical brain regions (see Section 2.1.3). Functional imaging data also provides evidence for the developmental changes that are implicated in the dual-systems accounts. During middle childhood and adolescence, neural responses to cognitive control tasks shift from a diffuse to focal pattern of activation, with increased activity in task-related regions – such as the lateral

and medial PFC – and diminished activation in regions that are not critically involved in the task (Bunge & Wright, 2007; Crone, 2009; Klingberg, Forssberg, & Westerberg, 2002). This diffuse pattern of activation in PFC contrasts with the hyperactivity seen in subcortical regions (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Guyer et al., 2008; Hare et al., 2008). Research on reward processing clearly indicates a heightened responsivity to reward during adolescence (Ernst et al., 2005; Galvan et al., 2006; Somerville, Hare, & Casey, 2011). For example, Galvan et al. (2006) have found increased activity in the nucleus accumbens during a reward task in adolescents compared to both children as well as adults. But also positive emotional stimuli, such as happy faces, have been shown to result in increased activity in the ventral striatum (Somerville et al., 2011). Differences in amygdala activation have also been reported, with adolescents showing higher amygdala activity relative to children and adults (Ernst et al., 2005; Hare et al., 2008).

Even though dual systems accounts offer an interesting and helpful framework for studying the interplay of emotional and cognitive factors during adolescence, this model also includes some limitations. One of these limitations is that no distinction is made between the impact of emotional and motivational stimuli. Although emotion and motivation are related to one another and are both important in guiding goal-directed behaviour, some researchers point to differences between these two constructs (Chiew & Braver, 2011; Rosemann, 2008). Whereas motivations are more directly linked to action tendencies, emotions could be considered as internal states determining goal prioritization (Chiew & Braver, 2011). However, these differences are not taken into account in dual-systems models. Another limitation concerns the model's emphasis on appetitive cues, while less attention is devoted to aversive stimuli. Furthermore, authors who have tried to integrate both types of stimuli into the dual-systems model (Somerville et al., 2010) propose that they rely on a common emotional/motivational system – mediated by the ventral striatum and to a lesser extent the amygdala – exhibiting hypersensitivity to both appetitive and aversive cues. However, neurobiological findings on amygdala activation in response to aversive stimuli are mixed. Although exaggerated amygdala responses have been reported in response to fearful compared to neutral faces (Guyer et al., 2008; Monk et al., 2003), another study has found decreased amygdala activity during the omission of reward in

adolescents compared to adults (Ernst et al., 2005). To account for these findings, Ernst et al. (2006) propose a distinction between a positive, approach-related and a negative, avoidance-related system instead of postulating a common emotional/motivational system for both appetitive and aversive stimuli. This triadic model of adolescent motivated behaviour is discussed in detail below.

2.2.2 Triadic model

According to the triadic model, three functional neural systems underlie adolescent motivated behaviour, i.e. an approach-related, an avoidance-related and a regulatory control system. The distinction between a positive, reward-driven, approach system and a negative, harm-avoidant module, which distinguishes the triadic model from dual-process accounts, is based on the biopsychological personality theory of Gray (1970). In this theory, Gray suggested that two systems determine individual differences in human behaviour. The Behavioural Activation System (BAS) is the driving force behind approach behaviour and is sensitive to potential rewards, while the Behavioural Inhibition System (BIS) is sensitive to punishment and potentially dangerous or unfamiliar stimuli, driving us to avoid aversive cues. The triadic model has applied Gray's BIS/BAS theory to adolescent behaviour, suggesting that in this age group the equilibrium between both motivational systems is altered. In a potentially rewarding context, the balance between these systems is thought to be tilted towards reward-driven (approach) behaviour at the expense of avoidance behaviour. This shift could be due to hypersensitivity of the reward system, decreased sensitivity to punishment and/or an immature supervisory system. The latter forms the third node of the triadic model, i.e. the regulatory control system, which is supposed to modulate the equilibrium between the two motivational systems. This node is similar to the cognitive control system as proposed by dual-systems models. Due to its immaturity, this control system is unable to restore the balance between the approach and avoidant system.

The three nodes that are part of the triadic model are supported by different neural networks that are partly overlapping and heavily interconnected (see Figure 2). The approach system is thought to rely on the ventral striatum, especially the nucleus accumbens, a structure implicated in reward processing (Costa, Lang, Sabatinelli, Versace, & Bradley, 2010; Phan, Wager, Taylor, & Liberzon, 2004). The avoidance

module is associated with amygdala circuits, which are responsive to threat and other negative cues (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Davis & Whalen, 2001; Rosen, 2004). Similar to the dual-process accounts, the control module consists of prefrontal structures, (especially the medial and ventral PFC) responsible for the "top-down" control of the motivational systems (Miller, 2000).

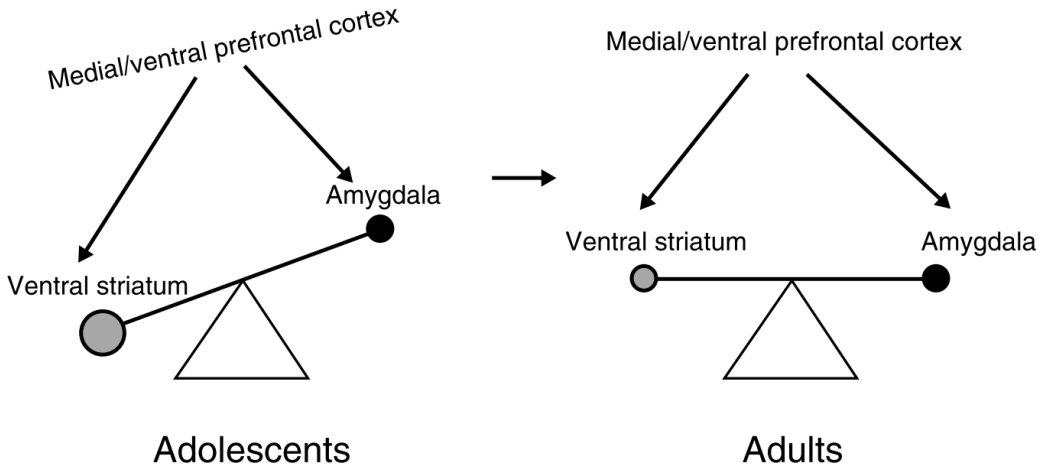

Figure 2. The modules of the triadic model with their respective neural circuits (taken from Ernst et al., 2006)

2.2.3 The dual-process and triadic model: merits and shortcomings

Both dual-process accounts and the triadic model have inspired a wealth of research aimed at understanding the neuropsychological basis of adolescent behaviour. One field of study where these theories have been especially fruitful is in the context of reward-related behaviour. Both theories hypothesize a hypersensitivity to incentives combined with difficulties inhibiting or suppressing the tendency to obtain this reward, boosting approach behaviour (at the expense of taking into account possible negative consequences of this action). As mentioned earlier (see section 2.2.1), what they do not address is whether emotional and motivational factors are expected to influence cognitive control in the same manner. In the triadic model, the term 'motivation' is used to refer to the approach system and is linked to reward, while 'emotion' is associated with the avoidance system. Recently, this distinction has been challenged by Luciana and Segalowitz (2014), stating that linking approach to motivation and emotion to avoidance is confusing, and suggesting that both the approach and avoidance system are associated with emotion and motivation.

Developmental research examining how affect impacts cognitive control has mostly used motivational manipulations, i.e. reward and/or punishment, while studies involving emotional manipulations, such as mood induction or exposure to affective pictures, are more scarce. Nevertheless, recent attempts have been made to bridge this gap in the literature. A popular paradigm in the developmental literature to examine emotional influences on cognitive control, and more specifically inhibitory control, is the go/no-go task. Emotional versions of this task have been used in children, adolescents and adults (Cohen-Gilbert et al., 2014; Cohen-Gilbert & Thomas, 2013; De Houwer & Tibboel, 2010; Hare et al., 2005; Hare et al., 2008; Ladouceur et al., 2006; Schel & Crone, 2013; Tottenham, Hare, & Casey, 2011). For example, Cohen-Gilbert and Thomas (2013) presented participants between 11 and 25 years of age with a series of letters on a background of positive, negative, neutral or scrambled IAPS pictures. They were asked to press a button for all letters except X, while ignoring these irrelevant emotional pictures. Negative backgrounds were found to slow down responses in all age groups, but early adolescents seemed especially vulnerable to emotional distraction, but only for negative and not positive stimuli.

Instead of presenting emotional stimuli in the background during a classic go/no-go task, other researchers have examined the impact of relevant emotional information on inhibitory control by making the affective value of the stimulus the target feature (Cohen-Gilbert et al., 2014; Somerville et al., 2011; Tottenham et al., 2011). Tottenham et al. (2011) compared performance of children (5-12 years), adolescents (13-18 years) and adults (19-28 years) on a task where happy, fearful, sad and angry faces served as the go/no-go stimulus, in combination with neutral faces. Although false alarm rates were higher in response to emotional compared to neutral no-go stimuli in all age groups, this effect decreased with age suggesting a developmental increase in emotion regulation capacities. Furthermore, adolescents were found to respond faster to emotional compared to neutral go-stimuli indicating a tendency to approach both positive (happy faces) and negative (fearful, sad and angry faces) stimuli, as suggested by dual-process models (Casey et al., 2010; Galvan, 2010; Somerville & Casey, 2010; Somerville et al., 2010; Steinberg, 2008).

The discrepancy in findings in the abovementioned studies clearly underscores the importance of taking into account the relevance of emotional information for the

task goal. One recent study has directly compared inhibitory control for relevant and irrelevant emotional information (Schel & Crone, 2013). Two variants of a go/no-go task with emotional face stimuli (happy, fearful and neutral faces) were administered from participants within an age range of 6 to 25 years of age. While emotion was the target feature in one version, the relevant dimension in the other go/no-go task was the color of the faces. Relevant emotions had a strong impact on response inhibition in all age groups, whereas irrelevant emotion did not affect inhibitory control. In the emotional go/no-go task responses on go-trials were faster for happy compared to fearful faces. False alarm rates were higher on trials with fearful compared to happy faces across all age groups. This finding is not in line with results from Somerville et al. (2011), who found decreased inhibitory control for happy faces in mid-adolescence. Furthermore, in the latter study, this dip in impulse control to appetitive cues was accompanied by enhanced ventral striatum activity, as hypothesized by dual-process models (Casey et al., 2010; Galvan, 2010; Somerville & Casey, 2010; Somerville et al., 2010; Steinberg, 2008).

Since dual-process models are mainly used to explain the increase in risk-taking behaviour during adolescence, most studies within this framework have focused on inhibitory control, while other cognitive control processes, such as WM, have been largely neglected. Given that inhibition and WM have differing developmental trajectories (Luna et al., 2004), an intriguing question is whether emotion will impact these competences differently. In the next section, we will first discuss findings with regard to emotional WM in adults to indicate why similar research in adolescent might be especially fruitful. Subsequently, we will discuss the limited evidence on emotional WM in adolescent samples.

3. EMOTIONAL WORKING MEMORY

3.1 Evidence in adults

Perlstein et al. (2002) were the first, to our knowledge, to investigate the influence of emotional content on WM performance. Using a delayed match-to-sample task with pleasant, unpleasant and neutral IAPS pictures, they found that the increase in dlPFC activation during the delay varied according to the valence of the stimuli.

Activity in this WM-related region was larger for pleasant and smaller for unpleasant pictures, as compared to neutral stimuli, and behavioural performance (in a larger sample) followed this effect, with better WM performance for positive and impaired WM performance for negative pictures. Kensinger and Corkin (2003) followed-up on these findings in a series of behavioural studies, and only found an effect on an n-back task using faces. More specifically, participants responded slower to fearful than neutral faces. Other WM tasks (e.g. word span tasks and an n-back task with words) did not show emotional interference effects. Increased saliency of faces compared to words might explain this selective effect, given that faces are biologically relevant stimuli (Rellecke, Palazova, Sommer, & Schacht, 2011; Vuilleumier, 2005). Indeed, several studies have replicated the finding that emotional facial expressions impact WM, although findings about valence-specific effects are mixed. While some studies have shown enhanced performance for positive faces (D'Argembeau & Van der Linden, 2007; D'Argembeau, Van der Linden, Etienne, & Comblain, 2003; Fales, Becerril, Luking, & Barch, 2010), others have reported improved performance for negative faces (Jackson, Linden, & Raymond, 2014; Kensinger & Corkin, 2003).

In addition to the abovementioned studies where emotional stimuli were central to the task goal, other researchers have examined the role of emotional distraction on WM. For example, Dolcos and McCarthy (2006) have compared the effect of emotional and non-emotional distractors presented during the delay interval of a WM task. Activity in typical WM regions, such as the dlPFC and lateral parietal cortex (LPC), was found to depend on the distractor type. Emotional distractors during the delay resulted in a relative deactivation of these WM regions, and increased activity in regions traditionally implicated in emotional processing, such as the amygdala and vlPFC. Moreover, this pattern was related to impaired performance, suggesting that activity in ventral emotional regions disrupts activation of the dorsal system linked to WM maintenance.

Since WM processes are thought to play an important role in the etiology of depression, and more specifically rumination (Joormann, Yoon, & Zetsche, 2007), a number of studies have compared maintenance of (negatively) valenced information in WM in healthy and depressed adults. Indeed, Joormann and Gotlib (2008) have shown that depressed individuals had more difficulties removing negative material from WM

than controls, even when compared to never-depressed individuals in a sad mood. Research by Levens and Gotlib (2010) led to the same conclusion, with depressed individuals showing a tendency to keep negative material active in WM, while healthy controls tended to keep positive information in mind.

WM is also an important component implicated in cognitive theories of anxiety, such as Attentional Control Theory (ACT; Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011). ACT builds on the WM model of Baddeley (1986), which divides WM into three components: 1) the phonological loop, responsible for rehearsing and storing verbal content, 2) the visuo-spatial sketchpad, underlying the processing and maintenance of visual and spatial information, and 3) the central executive, which is a supervisory attentional system controlling information processing. According to ACT, anxiety will have an impact on the central executive, while effects on the other components are thought to be only modest. Furthermore, based on evidence indicating that the central executive can be subdivided into an inhibition, shifting and updating function (Miyake et al., 2000), recent accounts of the ACT suggest that anxiety impairs the inhibition and shifting function. These predictions have received considerable support thus far (for a review, see Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011).

Given the involvement of WM deficits in depression and anxiety, questionnaires measuring both are included in all empirical chapters in this thesis (**Chapter 3**-**5**) and correlations with performance or neural activation are examined. Furthermore, in **Chapter 5**, we examined WM for emotional information in students at risk for developing mood disorders.

3.2 Emotional working memory in adolescents

As noted before, studies examining emotional WM in adolescents are rather scarce. In a couple of studies, Ladouceur and colleagues have investigated the interference of irrelevant affective information while performing a standard WM task (Ladouceur et al., 2005; Ladouceur et al., 2013; Ladouceur et al., 2009; Tavitian et al., 2014). In a study using neutral, positive or negative IAPS pictures as distractors, healthy controls were more easily distracted by positive backgrounds, as suggested by longer reaction times, while depressed or comorbid anxious/depressed adolescents performed

worse when negative background pictures were used (Ladouceur et al., 2005). In a similar paradigm that has been used in several studies (Ladouceur et al., 2013; Ladouceur et al., 2009; Tavitian et al., 2014) happy, neutral and angry faces were shown as distractors, instead of IAPS pictures. Results showed that high anxious participants responded slower on a high load condition with fearful faces (Ladouceur et al., 2009), and that depressed adolescents performed worse for neutral faces independent of memory load (Tavitian et al., 2014). Together, these findings indicate perturbed processing of emotional information in both anxious as well as depressed adolescents. Furthermore, the finding that healthy controls were more easily distracted by positive backgrounds is in line with theories proposing hypersensitivity to (positive) emotional information during adolescence (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008). However, it is unclear whether this pattern is also evident in adults, since none of these studies directly compared performance across these age groups.

In addition to these studies investigating interference of emotional distractors, Passarotti and colleagues (Passarotti, Sweeney, & Pavuluri, 2010; Schenkel, Passarotti, Sweeney, & Pavuluri, 2012) have examined how relevant affective content is manipulated in WM. Healthy controls were found to activate emotion regulation and WM regions more for angry compared to neutral faces, while activation was diminished in these regions for the happy versus neutral faces. Unfortunately, the relationship between this activation pattern and behavioural performance was not examined thus limiting the interpretation of this finding.

To conclude, while affective modulation of WM processes have clearly been shown in adults, evidence in adolescents is very limited. Furthermore, these studies have focused on clinical populations, leaving the development of emotional WM in healthy adolescents understudied. Moreover, previous studies have often used a wide age range and have not compared adolescents' performance to that of adults. Thus, it is unclear whether the patterns observed in healthy controls are general mechanisms also present in adulthood or whether they are specific to adolescents.

4. RESEARCH OBJECTIVES AND OVERVIEW OF THE CHAPTERS

The main goal of this dissertation was to study the influences of (ir)relevant emotional stimuli on cognitive control, and more specifically WM processing, in adolescents and adults. Although the last decade has seen an increased interest in emotion-cognition interactions in adults, there is no agreement on the neurological underpinnings. In **Chapter 2** we reviewed 43 fMRI studies reporting a significant impact of emotion on cognitive control. To establish which regions were commonly activated, we performed an activation likelihood estimation (ALE) meta-analysis on the reported neurological coordinates. Additional analyses also examined whether the relevance of the emotional stimuli and the behavioural performance influenced the underlying neural circuitry.

Based on a literature review in adolescents, the focus of the remaining chapters in this thesis was narrowed down to emotional influences on WM. As outlined in this introductory chapter, the majority of studies in the developmental literature on the interplay between affect and cognition have investigated how emotion modulates inhibitory control, while the impact on WM has been largely neglected. Nevertheless, research in adults has clearly shown that maintaining emotional information online is an important factor in well-being (Pe, Koval, et al., 2013), optimism and pessimism (Levens & Gotlib, 2012), rumination (Pe, Raes, Koval, et al., 2013) but also in the development of psychopathology, especially depression (Levens & Gotlib, 2010). Thus, similar research in adolescents might increase our understanding of the neurobiological and behavioural mechanisms underlying normative development as well as the increase in emotional instability and rise in the incidence of depression during adolescence.

Another gap in the literature that was addressed in this thesis concerns the relevance of emotional information within the cognitive control task. While previous studies have often overlooked the exact role of the affective material within the cognitive task that participants were asked to perform, the relevance of this information is explicitly manipulated in the studies described in **Chapter 3 and 4**. In these chapters, we compared the performance of adolescents and adults on an emotional face WM task where attention was either directed to the expression of the face (happy, neutral or angry), or to an irrelevant dimension, i.e. the gender of the face.

Thus, in the latter condition, participants had to neglect the facial expression. **Chapter 3** describes a behavioural study, while **Chapter 4** is an fMRI study. In the latter, we investigated activations in the regions identified in the meta-analysis discussed in **Chapter 2**.

In **Chapter 5**, we wanted to explore how adverse events during childhood or adolescence might impact cognitive processing of emotional information. Previous studies have shown that a stressful childhood/adolescence is related to reduced cognitive control abilities on the one hand and perturbed emotional processing on the other hand (Mueller et al., 2012), and that these traumatic events constitute a risk factor for developing psychopathology, such as depression, later in life (Coffino, 2009). Given the importance of emotional WM deficits in the etiology of depression (Joormann & Gotlib, 2008; Levens & Gotlib, 2010), we set out to investigate whether deficient WM processes in the face of emotional information could underlie this heightened risk for developing depression following childhood trauma. In this study, we used a task measuring spatial WM for irrelevant emotional faces.

Finally, all findings reported in the this thesis are integrated and synthesized in the General Discussion (**Chapter 6**).

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CHAPTER 2

PROBING EMOTIONAL INFLUENCES ON COGNITIVE CONTROL: AN ALE META-ANALYSIS OF COGNITION EMOTION INTERACTIONS[1]

ABSTRACT

Increasing research documents an integration of cognitive control and affective processes. Despite a surge of interest in investigating the exact nature of this integration, no consensus has been reached on the precise neuroanatomical network involved. Using the activation likelihood estimation meta-analysis method, we examined 43 functional magnetic resonance imaging (fMRI) studies (total number of foci = 332; total number of participants, N = 820) from the literature that have reported significant interactions between emotion and cognitive control. Meta-analytic results revealed that concurrent emotion (relative to emotionally neutral trials) consistently increased neural activation during high relative to low cognitive control conditions across studies and paradigms. Specifically, these activations emerged in regions commonly implicated in cognitive control, such as the lateral prefrontal cortex (inferior frontal junction, inferior frontal gyrus), the medial prefrontal cortex, and the basal ganglia. In addition, some areas emerged during the interaction contrast that were not present during one of the main effects and included the subgenual anterior cingulate cortex and the precuneus. These data provide new evidence for a network of cognition emotion interaction within a cognitive control setting. The findings are discussed within current theories of cognitive and attentional control.

[1] Based on Cromheeke, S., & Mueller, S.C. (2014). Probing emotional influences on cognitive control: an ALE meta-analysis of cognition emotion interactions. *Brain Structure & function, 219*, 995-1008.

INTRODUCTION

Contrary to a long tradition of research, increasing evidence suggests that "cold" higher-order cognitive systems and "hot" affective, emotional systems do not operate independent of one another (Banich et al., 2009; Gray, Braver, & Raichle, 2002; Mueller, 2011a; Pessoa, 2008). Supported by these findings, recent theoretical views have challenged the common assumption of a "modular" view of neural processing, i.e., that emotion on the one hand and cognition on the other hand occupy distinct anatomical areas in the brain (Pessoa, 2008). Instead, these theories propose that affective and cognitive mechanisms are processed in shared underlying neurocircuitry (Pessoa, 2008; Shackman et al., 2011). However, the precise nature of this integration and its underlying neuroanatomy are still unclear.

Cognitive control, a skill commonly associated with 'cold' higher-order processing, is essential for goal-oriented behavior and linked to function of the dorsolateral prefrontal cortex (dlPFC) (Miller & Cohen, 2001) and the dorsal anterior cingulate cortex (dACC) (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). In a first study that examined how emotion and cognitive control integrated, Gray et al. (2002) reported that the dlPFC response during a working memory task was modulated by prior positive or negative mood induction. However, responsivity of cognitive control to emotional material has also been reported in other brain regions including the anterior insula (Levens & Phelps, 2010), amygdala (Van Dillen, Heslenfeld, & Koole, 2009), striatum (Padmala & Pessoa, 2010), or parietal cortex (Schulz et al., 2009) suggesting a contribution of regions outside the prefrontal cortex in this process. Despite an increase in fMRI work on this topic, no consensus has been reached on the precise neural networks involved in the interaction between cognitive control and emotion. Part of this problem is that different emotional dimensions (e.g., prior mood induction, emotional distraction) have been intermixed with a variety of "classic" cognitive control tasks (e.g, n-back working memory task, the Stroop task, or the go/no-go task)(c.f. Table 1 and Mueller, 2011b). Yet, knowledge of regions of interaction and integration are theoretically important to define the circumstances under which emotion and cognitive control can conjointly modify behavior or operate in a hierarchical order of processing at both the behavioral and neural level.

As alluded to above, one distinctive problem in the identification of regions of integration is the variability of processes involved. Cognitive control is an umbrella term for a variety of separable executive processes including set-shifting, inhibition, maintenance and updating of working memory, or error monitoring (Banich et al., 2009; Miyake et al., 2000). Emotion, by comparison, is varied in valence (e.g., positive or negative), can occur during (Dolcos & McCarthy, 2006b; Goldstein et al., 2007; Habel et al., 2007) or prior to (Deckersbach et al., 2008; Hart, Green, Casp, & Belger, 2010) cognitive control, and can have distinct motivational significance (approach-related vs. avoidance-related) (Roseman, 2008; Sutton & Davidson, 1997). Inconsistency in findings occurs at several levels. For example, whilst most studies seem to report an increase in the BOLD response during the critical interaction condition (Blair et al., 2007; Pereira et al., 2010), other studies have reported a paradoxical signal decrease (Dolcos & McCarthy, 2006b; Fruhholz, Fehr, & Herrmann, 2009). Discrepancy also extends to the behavioral outcome of dealing with emotion during a standard cognitive control task. While some authors have reported that concurrent emotion impairs cognitive control (Dolcos & McCarthy, 2006a; Wessa, Heissler, Schonfelder, & Kanske, 2012), others suggest a boost of cognitive control performance in the presence of affective material (Fruhholz et al., 2009; Kanske & Kotz, 2011). A third factor that may impact the integration process is the relevance of the emotion for the current task. In some tasks, the affective dimesion is task-relevant, i.e., participants need to pay close attention to the affective stimulus to solve the task (e.g., Chechko et al., 2009; Goldstein et al., 2007). In other studies, the affective dimension was task-irrelevant, i.e., the affective stimulus served as a distractor (e.g., Hart et al., 2010; Wessa et al., 2012). These circumstances, alone or in combination, may have so far prevented a transparent picture of how emotion affects critical cognitive control processes. It is thus unclear whether a) the presence of emotion boosts cognitive control due to higher biological significance or whether b) emotion interferes with self-regulatory control, which leads to increased recruitment of cognitive control areas to maintain equilibrium.

This study aimed to clarify these inconsistencies by virtue of a meta-analytic procedure, the Activation Likelihood Estimation (ALE) meta-analysis method (Eickhoff et al., 2009; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Usage of the meta-analysis method

has several advantages. First, we wanted to identify consistently activated brain regions during interactions between emotion and cognitive control across tasks and affective dimensions. Second, this identification would provide necessary empirical support across studies for or against current theories of emotion cognition integration (c.f. Gray, 2001; Pessoa, 2008). Third, a survey of the current literature would identify gaps and engender essential questions in need of pursuit to better characterise integrative processes between the affective and control systems. Of note, given that previous meta-analyses and reviews have examined the cognitive control of emotion (i.e., emotion inhibition, cognitive re-appraisal) (Bush, Luu, & Posner, 2000; Diekhof, Geier, Falkai, & Gruber, 2011), the present study focused selectively on the influence of emotion on 'cold' cognitive control, not vice versa. To this aim, a meta-analysis was performed on studies that specifically reported significant interactions between emotion and cognitive control.

METHOD

Study selection

Relevant studies were identified through a systematic database search for peer-reviewed articles published between January 1995 and September 2012 on ISI Web Of Knowledge (Thomson Reuters, NY, USA) and PubMed. Searches were conducted with the keywords "fMRI" or "functional magnetic resonance", in combination with one or two of the following search terms: "emotion", "affective, "reward", "motivation", "cognitive control", "cognitive interference", "emotional interference", "emotion-cognition", "cognition-emotion", "inhibition", "Stroop", "flanker", "go nogo", "stop signal", "task switching" and "working memory". In addition, the reference lists of the selected articles were used to identify additional relevant papers. This search yielded 1347 papers (see Appendix 1 for a flowchart of detailed selection and reasons for exclusion).

Studies were required to fulfill the following criteria for inclusion: 1) Since we were interested in the neural correlates of emotion-cognition interactions only fMRI studies were included; 2) Selected studies had to report [x, y, z] coordinates for interaction effects between emotion and cognitive control in standard stereotactic

space (either Talairach or MNI). Studies not reporting specific coordinates were excluded; 3) Only data from experiments in healthy adults were included. However, coordinates from healthy controls in patient studies were also included if separate within-group contrasts were provided; 4) To avoid bias in the data we excluded studies using an anatomical region-of-interest (ROI). Studies performing a whole brain (WB) analysis or functional ROI were included. In total, 43 fMRI studies (total number of foci = 332; total number of participants, N = 820) were included in the final meta-analysis (Table 1). Foci that were located outside the mask of gray matter used by GingerALE 2.1 were excluded from all analyses.

Contrast selection

This study sought to examine how emotion modulates neural activity during cognitive control performance. To this end, studies reporting an interaction between a cognitive control task and an emotional context were selected. However, since statistical interaction effects could be driven by both activations and deactivations, because of the difficulty in interpreting deactivation and because few studies have reported such deactivations, only contrasts of increased activation in the emotional cognitive control condition were included (cf. details of contrast selection per study in Table 1). This inclusion criterion also facilitated interpretation.

In addition to examination of general brain networks involved in emotion cognitive control integration, two additional subanalyses were performed. First, studies were divided into those where emotional stimuli were task-relevant or task-irrelevant, i.e., whether the stimuli needed to be attended to or served as distractors. Second, tasks were separated by their effects in the behavioral data, i.e., whether studies reported improvements or impairments during the emotional condition.

Although comprehensive meta-analyses on cognitive control (Derrfuss, Brass, Neumann, & von Cramon, 2005; Wager, Jonides, & Reading, 2004; Wager & Smith, 2003) and emotion (Shackman et al., 2011; Wager, Phan, Liberzon, & Taylor, 2003) in isolation are available in the literature, for the sake of internal consistency and to facilitate comparisons between regions, *main effects* of cognitive control and emotion processing were also computed.

Table 1. Overview of studies included in the meta-analysis

First Author	*Year*	*n*	*Experimental Paradigm*	*Emotional Stimuli*	*Behavioural interaction effect*	*Experimental contrast*
Beck	2010	31	delayed item recognition WM	liquid vs monetary reward	ME incentive condition (Money/Liquid > Baseline) during WM task	incentive > baseline during WM task
Beneventi	2007	12	1- and 2-back WM task	(scrambled) drawings of facial expressions	ns	facial expressions > scrambled drawings during n-back task
Blair	2007	22	modified affective stroop	IAPS (neg, pos, neu)	ns	negative (incongruent vs view) > neutral (incongruent vs view); positive (incongruent vs view) > neutral (incongruent vs view)
Brown	2012	20	emotional go-nogo task	IAPS (neu, aversive)	ns	(Aversive NoGo - Aversive Go) - (Neutral NoGo - Neutral Go)
Chechko	2009	18	emotional Stroop task	happy/fearful faces	/	emotionally incongruent > emotionally congruent (in controls); D: emotionally congruent > emotionally incongruent (in controls)
Chechko	2012	24	emotional Stroop task	happy/sad/fearful faces	task x congruency, F(1, 23) = 20, p < .001; stronger interference effect in the emotional vs non-emotional task	emotional (incongruent > congruent) - non-emotional (incongruent > congruent); D: non-emotional (incongruent > congruent) > emotional (incongruent > congruent)
Deckersbach	2008	17	2-back WM task	mood induction (autobiographical scripts)	RT in 2-back: no mood induction < neutral state induction < negative state induction	sad > neutral during 2-back task
Dolcos	2006	15	delayed WM for faces with emotional scene distraction	IAPS plus in house	ME of distracter type (worse performance for emotional compared to neutral and scrambled distractors)	Emo > Scram, Emo > Neu; D: Scram > Emo, Neu > Emo
Dolcos	2008	14	delayed WM for faces with emotional face and scene distraction	IAPS plus in house	ns	neg > face, neg > neu and scramb face > face during WM task; D: face > neg, face > scramb face
Erk	2007	12	item recognition task (low vs high load), IAPS during delay	IAPS (neg, pos, neu)	no load x valence interaction; within load 6: better performance during positive, negative and no picture vs neutral condition	negative (load1+6) > neutral (load 1+6) inclusively masked with load 6 (neg+neu)>load1(neg>neu)
Fruehholz	2009	20	forced-choice categorization of neg, neu and pos expressions with conflicting background (based on previous run)	neg, pos, neu faces	significant emotion x congruence interaction (F = 4.46; p = .018); stronger increase in RTs for incongruent trials with neutral expressions	negative (incongruent > congruent) > neutral (incongruent > congruent) + positive (incongruent > congruent); D: incongruent neutral > incongruent negative/positive
Goldstein	2007	14	go no-go emotional linguistic	neg, pos, neu words	RT significantly slower in no-go vs go within negative and positive valence condition, and trend within neutral valence	[(NegNoGo - NegGo) - (NeuNoGo - NeuGo)] and [(PosNoGo - PosGo) - (NeuNoGo - NeuGo)]
Gray	2002	14	emotional induction (short videos) followed by 3 back task	verbal and non verbal	word 3-back enhanced by pleasant state and impaired by unpleasant state, whereas face 3-back showed the reverse effect	integration-sensitive regions

Habel	2007	21	n-back WM task during neg. olfactory stimulation	letters, rotten yeast smell	olfactory stimulation x task interaction: F(1, 19) = 6.98; p = .02; RT 2-back neg > neu in AG	(2-back yeast masked with 0-back yeast) vs (2-back air masked with 0-back air)
Hart	2010	14	emotional priming during number stroop	IAPS (aversive, neutral)	emotionality x Stroop content: F(2,12) = 3.99; p = .047; slower RT on incongruent trials when preceding aversive vs. neutral stimulus	aversive incongruent > neutral incongruent
Kanske	2011	20	colour flanker task	neg, neu words	emotion x conflict: F(1,19) = 4.6; p < .05; reduced conflict for neg vs neu trials	negative (incongruent vs congruent) - neutral (incongruent vs congruent)
Kanske	2010	22	modified Simon task with emotional and neutral words	neg, pos, neu words	significant emotion (emotional, neutral) x conflict (congruent, incongruent) interaction; F(1,22) = 4.8; p < .05)	negative (incongruent vs congruent) - neutral (incongruent vs congruent)
Kellermann	2011	36	motor short-term memory task with emotional interference	IAPS (neg, pos, neu)	significant picture context (neu, pos, neg picture, green dot) x sequence length (4 or 6 items) interaction	emotion: 6 item > 4 item; emotional pictures (easy > difficult task) > neutral pictures (easy > difficult task)
Kouneiher	2009	16	contextual and episodic control task with low or high incentive	letters, monetary reward	/	contextual and episodic motivation with high vs low incentive
Krebs	2011	18	reward-modulated Stroop	color-words, monetary reward	ns	incongruent reward > incongruent no-reward
Krebs	2012	11	cued-attention paradigm (easy/hard) under reward and no reward	monetary reward	significant reward (reward, no-reward) x difficulty (easy, hard) interaction; F(1,13) = 9.05; p = .01; reward-related RT decrease more pronounced for easy targets	reward x difficulty interaction (high difficulty reward condition > other types)
Lee	2008	14	emotion expression interference task	dynamic facial expressions	/	incongruent - congruent during emotional interference task
Li	2009	33	stop-signal task	/	/	risk taking (RT decrease in post go go-trial) vs risk aversion (RT increase in post go go-trial)
Lim	2008	21	faces with superimposed letter arrays/ high load and low load, selective conditioning to some faces preceded experiment	neu, fearful faces	ns	easy fearful THREAT > SAFE; D: hard fearful THREAT < SAFE
Malhi	2005	12	emotional Stroop task	neg, pos, neu words	/	affective Stroop (neg+pos) > neutral Stroop
Mather	2006	26	emotional source-monitoring task	IAPS (high/medium/low arousal, pos/neg)	significant arousal induced impairment in source memory; F (1,15) = 10.16, p < .05	emotional > neutral; D: neutral > emotional (during WM task)
Melcher	2011	14	Stroop oddball task	IAPS (neg, neu)	trend for a cognitive and emotional manipulation; F(26, 2) = 3.212, p = .057	negative incongruent vs baseline
Mitchell	2006	28	lexical decision task	sentences with emotional content and prosody	significant effect of task condition: accuracy incongruent semantic condition < prosody-only condition; F(1, 27) = 194.72; p < .001	incongruent emotion > prosody only
Mittershiffthaler	2007	17	emotional Stroop task	sad, neu words	RT sad > neu words	negative Stroop > neutral Stroop

Mohanty	2005	17	emotional Stroop task	pos, neg, neu words	/	negative Stroop > neutral Stroop
Mullette-Gillman	2011	20	monetary oddball task	gain/loss	/	reward > no reward; D: no reward > reward (during oddball task)
Ochsner	2008	16	affective and cognitive versions of the flanker task	neg, pos, neu words	ns	incongruent > congruent during affective flanker
Padmala	2011	50	response conflict task under reward and no reward	monetary reward	significant motivation (reward, no reward) x congruency (neutral, congruent, incongruent) interaction; F (2, 98) = 12.11; p < .001	[(incongruent - neutral) during reward - (incongruent - neutral) during no reward]; D: [(incongruent - neutral) during no reward - (incongruent - neutral) during reward]
Park	2008	14	emotional Stroop task	in house (pos, neg)	significant interference effect of emotional incongruence	incongruence > congruence; D: congruence > incongruence (during emotional Stroop)
Pereira	2010	11	target detection task	IAPS and in house (neutral and unpleasant)	slower RT for target detection trials during unpleasant vs neutral blocks (p < .05)	unpleasant > neutral detection
Pochon	2002	6	n-back task under reward and no reward	monetary reward	ns	common activation of WM and reward; D: no reward > reward, inclusively masked with WM
Sagaspe	2011	12	stop-signal task	fearful, neu faces	significant emotion (neutral, fearful) x response condition (Go, StopRespond) interaction; F(1, 11) = 11.29; p = .006; RT StopRespond (failed stop) fearful > neu	StopInhibit Fear > StopInhibit Neutral
Savine	2010	16	task switching (gender:m/f or word: 1 or 2 syllables)	monetary reward	significant incentive x task-switching interaction; F(1, 15) = 11.38; p < .001	incentive x task-switching (incentive cue facilitation during task-switching > single task)
Schulz	2009	24	emotional go-nogo task	happy, sad, neu faces	trend for a ME of face emotional valence on correct inhibitions on no-go trials (happy/sad > neutral); F(2, 46) = 2.73; p = 0.08;	no-go > go in response to emotional faces
Taylor	2004	12	object-WM task with low or high load under reward and no reward	monetary reward	ns	high reward (high - low load) > low reward (high - low load)
VanDillen	2009	17	IAPS interspersed with simple (low load) or hard (high load) arithmetic problems	IAPS (neg, neu)	/	negative (complex > simple); D: negative (simple > complex)
Wessa	2012	30	arithmetic task with emotional distractors	IAPS (neg, pos, neu)	longer RT for emotional vs neutral distractor trials; F(1, 29) = 14.1; p < .001	arithmetic emotional - arithmetic neutral
Wingenfeld	2009	20	emotional Stroop task	neutral, general negative and individual negative words	RT individual negative words > neutral/general negative words	negative Stroop > neutral Stroop

ns = not significant; RT = reaction time; WM = working memory; A = activation; D = deactivation

Cognitive control contrasts included comparison of the condition with high vs. low control requirements (e.g., incongruent vs. congruent; NoGo vs. Go; task switch vs. task repeat, high vs. low working memory load) either in the neutral condition only or combined across valences. This resulted in 243 foci from 20 experiments. Similarly, for the main contrast of emotion, activation by emotional stimuli were compared to neutral stimuli (positive/negative vs. neutral or reward vs. no reward) collapsed across cognitive control conditions yielding 246 foci from 19 experiments. Of note, the "main effect" of emotion must still be understood within the context of a cognitive control experiment and other studies may be more suitable to identify "pure" emotion circuitry in the absence of a behavioral control task.

ALE analysis

To assess which brain regions were implicated in emotion-cognitive control integration, we used the ALE meta-analytic approach (Eickhoff et al., 2009; Turkeltaub et al., 2002) using GingerALE software (version 2.1 www.brainmap.org/ale). Unlike previous meta-analytic methods (e.g. based on anatomical labels or Brodmann areas (BAs)), this method provides a quantitative and objective measure of the convergence of neuroimaging findings. ALE was performed in Talairach and Tournoux (1988) stereotactic space and all coordinates reported in MNI space were converted to Talairach coordinates using the Lancaster transformation (Laird et al., 2010; Lancaster et al., 2007).

In an ALE-analysis, three-dimensional (Talairach or MNI) activation foci are extracted from relevant contrasts reported in selected neuroimaging studies. These peak activation coordinates are modelled as a three-dimensional Gaussian distribution with an estimated Full-Width Half-Maximum (FWHM) based on the number of participants in the study. Probability distributions within an experiment are merged into a "modelled activation" (MA) map, which reflects the probability for each (2 mm^3) voxel that at least one of the foci is located within that voxel. The individual MA maps are then combined into an ALE-map on a voxel-by-voxel basis, controlling for within-experiment effects (Turkeltaub et al., 2012). The ALE-map reflects the combined activation patterns across all experiments included in the meta-analysis. To determine statistical significance, the ALE-map is tested against an ALE null distribution map,

derived from a permutation procedure. To control for multiple comparisons, the ALE-map was thresholded at a false discovery rate (FDR) of $p<0.05$, corrected. Whereas other recent meta-analyses have commonly used a minimal cluster size of 100 mm^3 (Brooks et al., 2012; Swick, Ashley, & Turken, 2011; van der Laan, de Ridder, Viergever, & Smeets, 2011; Veldhuizen et al., 2011) we opted to use a slightly more conservative cluster size threshold of 200 mm^3 (c.f. Diekhof et al., 2011; Owen, McMillan, Laird, & Bullmore, 2005). ALE-maps were overlaid onto an anatomical T1-weighed image in Talairach space and displayed with Mango software (http://ric.uthscsa.edu/mango/). Anatomical labels were assigned using the Talairach Daemon (http://www.talairach.org/daemon.html) and the Human Brain Anatomy in Computerized Images Atlas (Damasio, 2005).

RESULTS

Influence of emotion on cognitive control (interaction effect)

The main ALE-analysis of significant interactions between emotion and cognitive control revealed 18 significant clusters (Table 2, Figures 1, 2), with the largest cluster (volume = 3960 mm^3) located in the medial and superior frontal gyrus (BAs 6/32). The maximum ALE value of 0.031 was observed in the right inferior frontal gyrus (IFG; cluster volume = 2488 mm^3). Other clusters included the right dlPFC (BA9), left IFG (BA 6), anterior insula, inferior parietal cortex (IPC), and bilateral subgenual anterior cingulate cortex (ACC; BA 25). In addition, activation was also found in subcortical regions such as the right amygdala.

Emotion-cognition interaction: the use of task-relevant vs. task-irrelevant emotional stimuli

An additional analysis was conducted to disentangle findings from studies in which emotional stimuli were relevant to the task and required attention or were irrelevant and served as distractors. When emotion was task-relevant (N = 19 studies, 161 foci), prominent clusters emerged in the medial and superior frontal gyrus (BA6), right putamen, bilateral subgenual ACC (BA25), bilateral fusiform gyrus (BA19/37), and

medial globus pallidus (Figure 3, orange clusters). When emotion was task-irrelevant (N = 14 studies, 112 foci), significant clusters emerged in the medial and superior frontal gyrus (BA 32), right dlPFC (BA9) and bilateral IFG (BA 6). Other clusters were located in the right amygdala, left insula, left inferior parietal lobule (IPL; BA 40) and right superior parietal lobule (SPL; BA 7) (Table 3 and Figure 3, purple clusters). To directly contrast both types of tasks, task-relevant activation clusters were subtracted from task-irrelevant activation clusters. Here, two interesting clusters were significant in the right dlPFC (BA 9; cluster volume = 816 mm^3) and IPL (BA 40; volume = 288 mm^3), implying that these areas were activated more if emotion was task-irrelevant as opposed to task-relevant. The reverse subtraction yielded no significant findings.

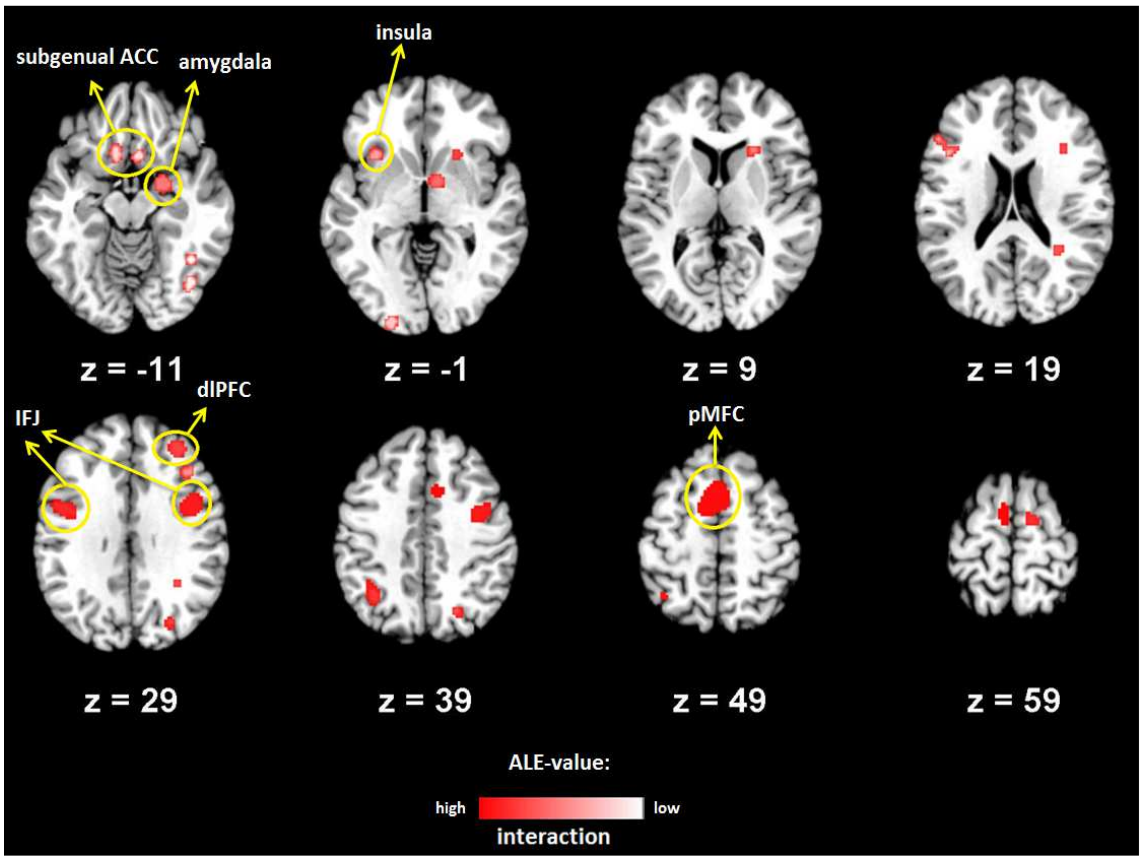


Figure 1. Significant activations during the interaction between emotion and cognitive control are presented on underlying anatomical T1 axial slices. ACC (anterior cingulate cortex), IFJ (inferior frontal junction), dlPFC (dorsolateral prefrontal cortex), pMFC (posterior medial frontal cortex). x, y, z coordinates are reported in Talairach space. Image activations were thresholded at $p < 0.05$ FDR. Strength of activation reflected by brightness of respective colour.

Table 2

ALE activation clusters associated with cognition emotion interactions, and their overlap with the main effect analyses

			Interaction					main effect of cognitive control				main effect of emotion			
					Peak				Peak				peak		
L/R	Anatomical label	BA	volume (mm^3)	ALE value ($x\ 10^{-3}$)	x	Y	z	ALE value ($x\ 10^{-3}$)	x	y	Z	ALE value ($x\ 10^{-3}$)	x	y	z
R	inferior frontal gyrus	6/9	2488	31	40	4	30	26,2	42	4	28	15,5	42	2	30
L/R	superior frontal gyrus/medial frontal gyrus	6/32	3960	28	0	10	48	32	2	14	48				
R	dorsolateral prefrontal cortex	9	704	24,8	32	40	28	21,1	36	38	28				
R	amygdala		512	22,1	22	-2	-10					37	22	-8	-10
L	inferior frontal gyrus	6	904	20,6	-40	0	30	36,7	-44	4	28				
L	occipital cortex (V1)	17	344	20	-20	-92	0								
R	medial globus pallidus		536	19	8	-2	-2					23	14	8	-2
R	putamen		496	18,7	20	16	4	16,1	14	12	-4	23	14	8	-2
L	inferior parietal lobule	7	840	18,5	-34	-56	44	24,8	-26	-58	46				
R	medial frontal gyrus	6	544	18,2	14	-6	56	26,7	26	-2	56				
L	subgenual ACC	25	312	17,6	-8	16	-10								
R	fusiform gyrus	37	200	17,2	40	-52	-12	15,8	38	-66	-12	24,5	42	-48	-16
L	insula		448	17,1	-30	16	-2	50,3	-32	20	2	17,2	-34	26	2
R	fusiform gyrus	19	256	17	40	-66	-10	15,8	38	-66	-12	24,5	42	-48	-16
R	precuneus	7/31	552	16,7	26	-74	26								
R	dorsolateral prefrontal cortex	9	464	16,1	38	26	28	21,1	36	38	28				
R	subgenual ACC	25	256	15,3	6	14	-12								
L	inferior frontal gyrus (pars triangularis)	45	384	14,8	-48	26	20	31,9	-44	6	28				

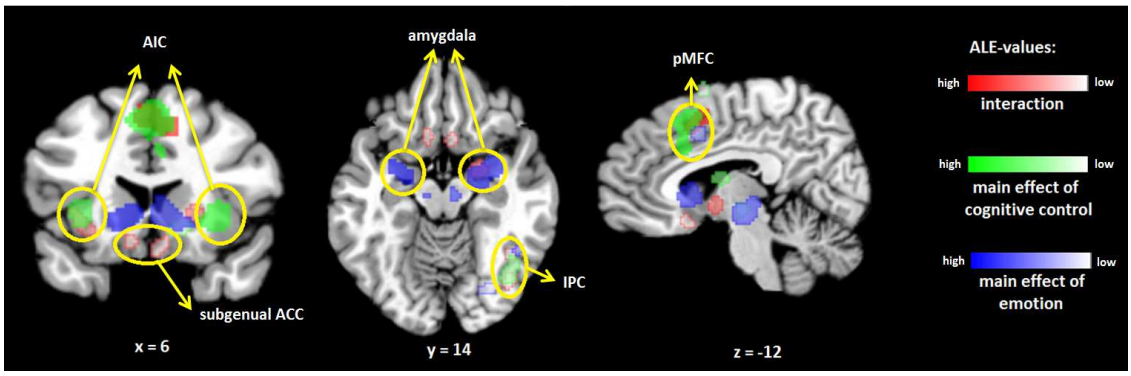


Figure 2. Significant activations of interaction (red color) overlaid with the main effects of cognitive control (green color) and emotion (blue color). Image activations were thresholded at $p < 0.05$ FDR.

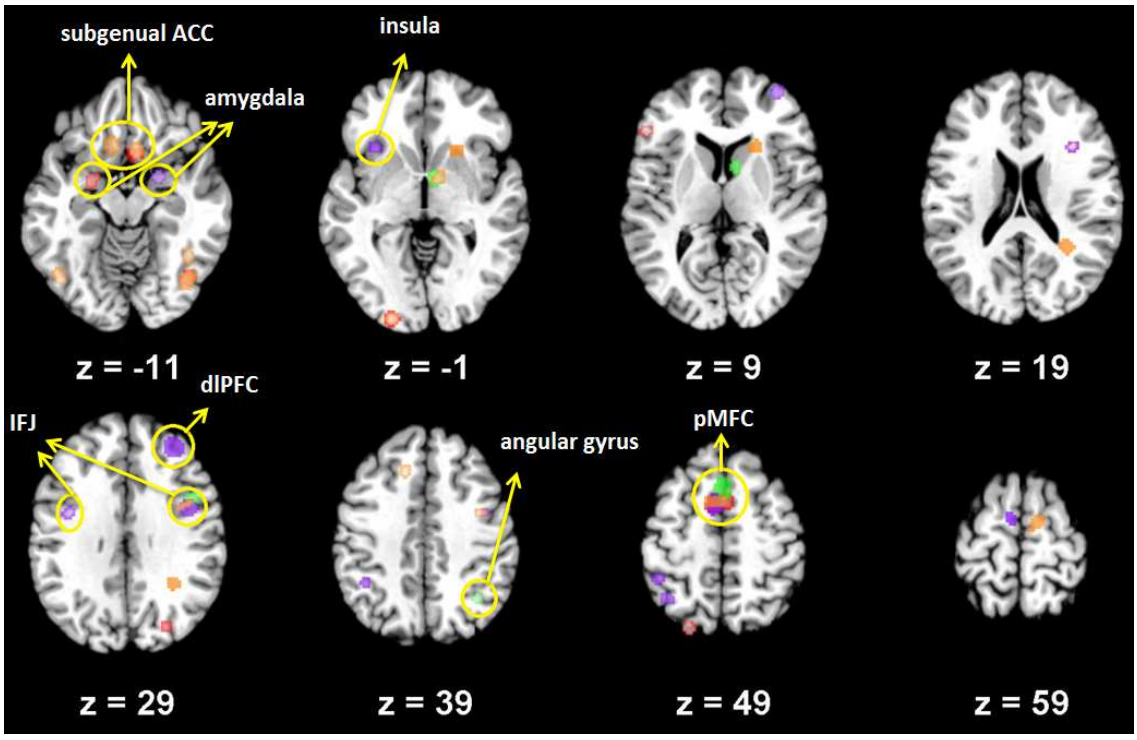


Figure 3. The figure shows significant activations as a response to task-relevant (orange color) and task-irrelevant (purple color) emotional stimuli. In addition, the figure also depicts the significant activation clusters for impaired (red color) and improved (green color) performance. x, y, z coordinates are reported in Talairach space. Image activations were thresholded at $p < 0.05$ FDR

Table 3. *Interaction analyses for studies where emotional stimuli are task-relevant vs. task-irrelevant*

L/R	Anatomical label	BA	Peak voxel coordinates			Cluster size (mm^3)	ALE value ($x\ 10^{-3}$)
			x	y	Z		
task-irrelevant emotional stimuli							
R	dorsolateral prefrontal cortex	9	30	40	30	1096	24,2
R	inferior frontal junction	6	40	2	28	784	20,0
L	medial/superior frontal gyrus	32	-6	8	44	1488	14,6
R	orbitofrontal cortex	10	36	54	8	312	14,4
R	amygdala		22	-2	-12	264	13,2
L	inferior frontal junction	6	-38	-2	32	264	12,8
R	superior parietal lobule	7	22	-62	54	240	12,6
L	inferior parietal lobule	40	-36	-56	46	256	12,1
L	insula	13	-32	18	2	432	11,8
L	inferior parietal lobule	40	-42	-44	48	376	11,3
R	middle frontal gyrus	6	42	0	44	200	11,2
task-relevant emotional stimuli							
R	putamen		20	16	4	760	18,6
R	fusiform gyrus	19	40	-66	-10	496	17,0
L	primary visual cortex	17	-20	-92	0	272	16,4
R	fusiform gyrus	37	40	-52	-12	256	15,9
L	medial/superior frontal gyrus	6	-8	6	52	736	15,8
R	medial globus pallidus		10	-2	2	360	15,7
L	subgenual ACC	32	-8	18	-10	408	15,6
R	medial/superior frontal gyrus	6	12	-6	56	512	15,6
R	subgenual ACC	25	8	16	-10	312	14,2
L	fusiform gyrus	37	-42	-64	-10	304	13,9
L	medial frontal gyrus	8	-12	26	42	216	13,2
R	inferior frontal junction	6	36	-2	36	296	11,6
contrast: task-irrelevant – task-relevant							
R	dorsolateral prefrontal cortex	9	26	44	28	816	
L	inferior parietal lobule	40	-40	-44	46	288	
contrast: task-relevant – task-irrelevant							
No clusters found							

Emotion-cognition interactions resulting in impaired vs. improved performance

The second additional analysis sought to discriminate between studies that have reported either improved or impaired behavioral performance during the emotion

condition of a cognitive control task. When the emotional manipulation resulted in improved performance (N = 10 studies, 52 foci), a large cluster in the superior frontal gyrus emerged (BA 6; volume = 1208 mm³; ALE-value = 0.0183). Other activations were located in the right IFG(BA 9), right hypothalamus, right caudate body and right angular gyrus (BA 39) (Table 4 top; Figure 3, green clusters). In studies where the presence of emotion impaired cognitive control (N = 14 studies, 121 foci) the largest and most significant cluster was also located in the superior frontal gyrus (BA 6; volume = 1248 mm³). Additional clusters were found in the left occipital gyrus (BA 17), bilateral precuneus (BA 7/31), right fusiform gyrus (BA 19), right subgenual ACC (BA 25), left IFG (BA 45) and left amygdala (Table 4 bottom; Figure 3, red clusters). A direct statistical comparison of studies reporting improved and impaired performance yielded no clusters.

Table 4. Interaction analyses for experiments resulting in impaired and improved performance

L/R	Anatomical label	BA	Peak voxel coordinates			Cluster size (mm³)	ALE value (x 10^{-3})
			x	y	z		
interaction analysis: improved performance							
L/R	superior frontal gyrus	6	0	12	50	1208	18,3
R	inferior frontal gyrus	9	42	7	30	480	17,3
R	hypothalamus/medial globus pallidus		6	-2	-2	368	12,8
R	caudate body		8	4	12	288	12,1
R	angular gyrus	39	34	-56	36	224	10,5
interaction analysis: impaired performance							
L/R	medial/superior frontal gyrus	6	2	6	50	1248	17
L	occipital gyrus	17	-20	-92	0	408	16,5
R	precuneus	31	26	-74	26	296	16,1
R	fusiform gyrus	19	40	-66	-10	328	15,1
R	subgenual ACC	25	4	14	-14	464	13,8
L	inferior frontal gyrus	45	-48	28	8	232	12,5
L	precuneus	7	-22	-74	50	256	12,4
L	amygdala		-22	-2	-12	296	12,3
L	medial frontal gyrus	6	-8	4	52	1248	11,5

Main effects of cognitive control and emotion

The meta-analysis of the main effects of cognitive control and emotion were conducted for easier comparison and served as internal control contrast. The main effect of cognitive control in the absence of emotion revealed 17 clusters. The highest ALE-scores and largest clusters were located in the bilateral insula (volume left = 1952 mm^3; ALE-value left = 0.0441; volume right = 3104 mm^3; ALE-value right = 0.0358), bilateral IFG (BA9; volume left = 2448 mm^3; volume right = 744 mm^3; ALE-value left = 0.0319; ALE-value right = 0.0224) and medial frontal gyrus (BAs 6/8; volume = 4448 mm^3; ALE-value = 0.0276). Other clusters were located in the bilateral supplementary motor area (SMA), bilateral SPL and right dlPFC (Figure 2, Appendix 2 top).

For regions activated during affective processing in the absence of a cognitive control condition, 13 significant clusters emerged. These local maxima emerged in several regions including the bilateral amygdala, superior temporal gyrus, insula, and medial ACC (Figure 2, Appendix 2 bottom).

DISCUSSION

This meta-analysis aimed to provide an objective overview of, and synthesize, discrepant findings on the influence of affective processing on cognitive control. Four main findings pertinent to the study goal emerged. First, several brain regions at both the cortical (e.g., IFG, dlPFC, IPL, subgenual ACC) and subcortical level (anterior insula, putamen, and amygdala) consistently responded to an emotional challenge within a cognitive control setting. Second, this analysis revealed two regions involved in the integration of emotion and cognition, i.e., a presence in the interaction but not in the main effects analysis, namely the bilateral subgenual ACC and the precuneus. Third, tasks where emotional stimuli served as distractors yielded increased activation in dlPFC and parietal cortex compared with tasks where emotion was relevant for the task at hand. Fourth, analyses also showed that behavioral performance patterns were associated with both similar and distinct regions. While activity in the superior frontal gyrus was increased irrespective of performance, clusters in 'emotional' regions (e.g. amygdala, subgenual ACC) were only found if performance was impaired. However, the

direct contrast between improved and impaired performance did not reveal any significant regions.

ALE meta-analysis of increased activation during emotion-cognition interactions

The interaction analysis revealed many clusters that are traditionally associated with both cognitive control (e.g. IFG, dlPFC) or emotion processing (e.g. amygdala, insula, striatum, subgenual ACC). Within the lateral PFC two clusters were identified, i.e. right dlPFC and inferior frontal junction (IFJ). Traditionally, the dlPFC is associated with maintaining the representation of task goals in working memory (Miller & Cohen, 2001). A previous meta-analysis of studies on set-shifting tasks, response reversal tasks, and Stroop paradigms has specifically implicated the IFJ, an area located within the vicinity of the junction between the inferior frontal and inferior precentral sulci of the lateral prefrontal cortex (PFC), in the updating of task representations (Brass, Derrfuss, Forstmann, & von Cramon, 2005). At the exact same coordinates as reported by that earlier meta-analysis, we not only found a main effect of cognitive control (thus independently replicating Derrfuss et al.'s finding in a different set of studies) but importantly showed that this region has an intimate relationship with emotional processes. Such data suggests that emotional material modulates the updating of task representations in the lateral PFC. It is conceivable that additional recruitment of this region in the presence of emotion could reflect increased updating of task goals to counteract the deleterious influence of emotional distractors on cognitive control. Likewise, consistent with a role of the right IFG in inhibition (Aron, Robbins, & Poldrack, 2004), increased responding of this region in the presence of emotion could mirror suppression of the emotional material to prioritize the executive task. However, significant interaction between emotion and cognitive control was not restricted to the lateral PFC.

Previous work has focused on the anterior midcingulate cortex (aMCC) as a potential site of integrating negative affect and cognitive control (Shackman et al., 2011). These authors suggest that the aMCC executes control in case of uncertainty of action. The present findings in posterior medial frontal cortex (pMFC) corroborate these suspicions but extended findings of interaction to regions beyond the frontal cortex.

One such region was located in the IPC) and within the bank of the angular gyrus [hIP1, human intraparietal area 1, (Choi et al., 2006)] as well as the anterior insula cortex (AIC). The IPC is attributed to be part of a fronto-parietal attention network, where it contributes to reorienting attention to task-relevant stimuli (Corbetta & Shulman, 2002; Liu, Banich, Jacobson, & Tanabe, 2004). In an interesting recent proposal, hIP1 projects to the anterior insula cortex (AIC) via the dorsal visual pathway (Uddin et al., 2010). There, the AIC detects the saliency of a stimulus and engages distributed attentional and higher-order control processes (Menon & Uddin, 2010). Consistent with these models of a parietal attention network (Corbetta & Shulman, 2002) and anterior insula function (Menon & Uddin, 2010), the presence of these areas in the current analysis suggests that emotional material modulates this cascade process of attentional processing. However, it is unclear whether presence of affective material receives preferential processing due to high salience or, alternatively, whether detection of the presence of salient material by the AIC engages additional control resources (e.g., dlPFC, ACC) to compensate distraction. Future work will need to address this issue.

A second finding of the meta-analysis revealed two regions, the bilateral subgenual cingulate and the dorsal posterior cingluate (dPCC)/precuneus, that were only significant during the interaction contrast but that did not emerge in either the cognitive control or emotion contrast alone. Although previous authors have suggested a special role of regions activated only in integration contrasts but not main effects (Gray, Braver et al., 2002), the present findings are ambiguous in that sense. For example, although the subgenual ACC did not appear in a main effect of emotion in the present study, this might be, to some extent, related to the fact that the analyses were conducted within a cognitive control background. In any case, the subgenual ACC has been identified as a major player in mood disorders, particularly depression (Drevets & Raichle, 1998) with strong projections to visceral and emotional control centers (Drevets & Savitz, 2008; Freedman, Insel, & Smith, 2000). Similarly, the dPCC (BA31) has also been implicated in mood disorders (Price & Drevets, 2010) and the precuneus (BA7) participates in episodic memory and self-referential processing (Cavanna & Trimble, 2006). Unfortunately, given the cluster size of the present activation and overlap among Brodmann areas, a precise distinction between the dPCC and precuneus cannot be made at this point. Given that the present results are located more laterally,

they are consistent with functional connectivity studies that have suggested intrinsic functional connections with cognitive and visual areas (Margulies et al., 2009). Taken together, these meta-analytic data suggest that the subgenual ACC and dPCC/precuneus may play a role in integrating affective processing with cognitive control in areas with links to visceral control anteriorily and cognitive and visual processing posteriorily. However, several factors are likely to modulate this processing such as the relevance of the emotional material to the task and/or the resultant effect on behavioral performance.

The impact of task-relevance on cognition-emotion interactions

Indeed, when emotional stimuli were relevant to the task and required attention, increased activation in visual areas (fusiform gyrus and primary visual cortex) and the subgenual ACC became apparent. Activation in visual areas could reflect prioritized processing of the salient, high-arousing emotional information (Mather et al., 2006). Given the subgenual ACC's strong links to both emotion centers (i.e., amygdala; Freedman et al., 2000) and visceral control centers (i.e., the hypothalamus, periacquaductal grey, and paraventricular nucleus of the thalamus) (Price & Drevets, 2010), this activation could reflect inhibition or suppression of emotion processing (e.g., Goldstein et al., 2007; Kanske & Kotz, 2011). By contrast, when emotional stimuli were task-irrelevant and merely served as distractors to the cognitive control task, activation clusters were found in both cognitive (dlPFC, IFJ, Me/SFG, IPL, SPL) and affective (insula, amygdala) regions. Of note, particularly activation in the right dlPFC and the IPL were increased in the irrelevant condition when directly compared to the relevant condition. Additional recruitment of these regions when emotion is irrelevant might reflect their role in counteracting the distracting effect of emotional stimuli by increasing task-specific activity (Wessa et al., 2012). In fact, if increased activity in cognitive control regions is indeed reflecting allocation of processing resources to task-relevant information, this activity should be related to performance improvements at the behavioural level. If additional recruitment of cognitive control regions is related to performance impairments, this increased activity could reflect efforts to inhibit the

emotional information, thus depleting processing resources that would otherwise have been allocated to the task.

The impact of task-performance on cognition-emotion interactions

Additional subanalyses on studies showing either performance improvement or impairment were carried out in order to evaluate both accounts. When performance was improved, consistent activation was limited to frontal regions (SFG and right IFJ) and the angular gyrus with no clusters in 'affective' regions. Activity in these regions presumably reflects increased task-specific activity and the recruitment of the fronto-parietal attention network to reorient attention to goal-relevant information. By contrast, when concurrent emotion impaired performance, activation clusters were found in both frontal (e.g. inferior, medial, and superior frontal gyrus) and limbic (e.g. amygdala, subgenual ACC) regions. This finding supports the idea that the inhibition of emotional information consumes processing capacity, diminishing the available resources for task-relevant processing and resulting in impaired performance. Although a dissociation between frontal regions and performance improvement on the one hand and frontal and limbic regions and performance impairment on the other hand is tempting, interpretation is limited given that no clusters emerged in the direct contrast between improvements and impairments. Direct comparisons of good vs. bad behavioural performance, possibly on a trial-by-trial basis, might reveal a link between behavioural outcome and limbic recruitment.

Future directions and limitations

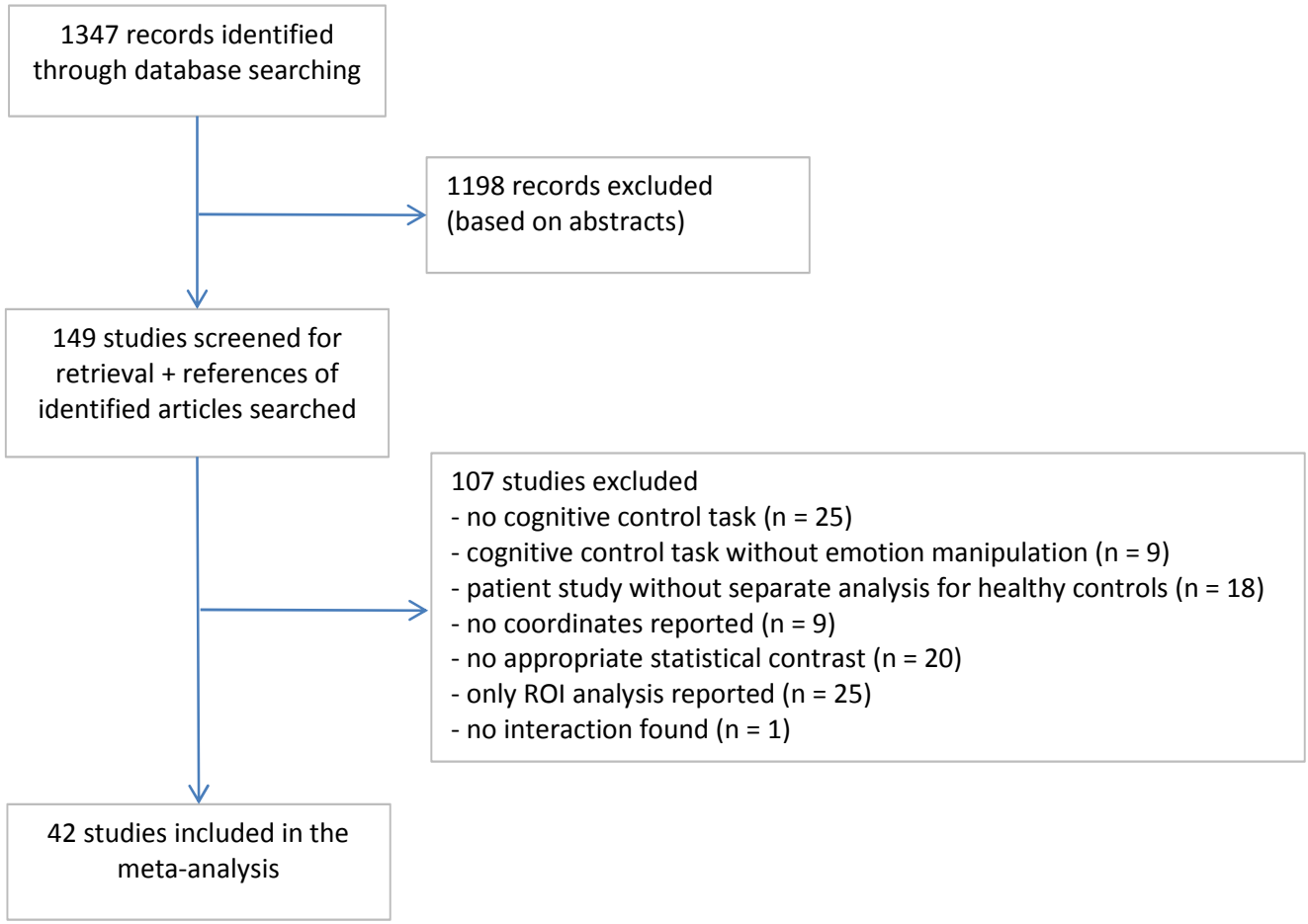
A last goal of this study was to identify gaps for further enquiry. Most of the included studies compared negative to neutral stimuli (N = 32 studies), while fewer studies looked at positive emotions (N = 13 studies). A differential impact of positive and negative valence on behavioral control seems plausible, given hypothesised hemispheric-specific processing in approach and avoidance-related behavior (Sutton & Davidson, 1997). Thus, future work should investigate neurobiological evidence for theoretical models of positive emotion on cognitive control processes and executive attention (Ashby, Isen, & Turken, 1999). In addition, given the multitude of paradigms reported in the literature, we could not disentangle the specific executive processes

and tasks used across studies. However, the purpose of this meta-analysis was to identify similarities across different tasks and processes. Future work can assess more specifically whether some of the reported effects are more likely to be influenced by specific tasks or executive processes. Similarly, given that only a minority of studies reported deactivation contrasts resulting in only 58 foci, we could not include these in the analyses. However, since deactivations can also offer valuable information, we encourage future studies to report both activations and deactivations.

Conclusion

In summary, this meta-analysis sought to find consistencies among an increasing number of studies investigating the influence of emotion on cognitive control. Increased neural activity during affective processing whilst performing a cognitive control task resulted in activation of a range of cortical and subcortical areas. However, these activations were partly modulated by task relevance of the affective stimulus and behavioral outcome suggesting that these factors should be taken into account when interpreting findings. Importantly, the results highlight two regions that were unique to the interaction contrast, the precuneus and the subgenual ACC. Future work is needed to define the precise functional contribution of each structure and clarify theoretical views on integrative processing.

Appendix 1: Flow chart of the selection process:



Appendix 2. Main effect analyses

L/R	Anatomical label	BA	Peak voxel coordinates			Cluster size (mm^3)	ALE value ($x\ 10^{-3}$)
			x	y	z		
			Cognitive control				
L	insula	13	-32	18	2	1952	44,1
R	insula		32	20	0	3104	35,8
L	inferior frontal gyrus	9	-44	6	28	2448	31,9
L/R	medial/superior frontal gyrus	6	2	14	48	4448	27,6
R	superior parietal lobule	7	32	-54	40	1992	25,1
L	superior parietal lobule	7	-26	-58	46	1784	24,7
R	inferior frontal gyrus	9	42	4	30	744	22,4
R	supplementary motor area	6	26	-2	54	728	21,8
R	dorsolateral prefrontal cortex	9	36	36	30	824	19,3
L	inferior parietal lobule	40	-42	-42	40	632	18,5
R	caudate		10	-8	14	704	17,5
L/R	red nucleus		4	-16	-4	440	16,8
R	putamen		14	12	-4	424	16,1
R	fusiform gyrus	19	38	-66	-12	688	15,8
L/R	superior frontal gyrus	6	6	6	64	264	15,8
L	supplementary motor area	6	-28	-6	54	416	15,2
R	cuneus/occipital gyrus	18	26	-90	0	528	14,9
			Emotion				
R	amygdala		22	-8	-10	3552	31,4
L	amygdala		-10	10	2	2584	28,4
R	putamen		14	8	-2	1912	22,9
L/R	red nucleus		6	-16	-8	408	21,4
L/R	medial ACC	32	6	8	40	808	20,4
R	fusiform gyrus		44	-48	-18	288	20,2
L	precentral gyrus	6	-30	-10	50	944	17,1
R	IPL/precuneus	7/40	32	-52	44	264	16,4
L	middle occipital gyrus	19	-46	-70	8	208	15,9
R	superior temporal gyrus	38	30	4	-30	240	15,2
L	IFG/insula	45	-34	26	4	240	15,2
R	declive		28	-72	-12	408	14,8
L	occipital	18/19	-36	-78	-4		14,6

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CHAPTER 3

THE POWER OF A SMILE: STRONGER WORKING MEMORY EFFECTS FOR HAPPY FACES IN ADOLESCENTS COMPARED TO ADULTS[1]

ABSTRACT

Theories of adolescent behaviour attribute increases in risk-taking and sensation seeking in this age group to a heightened sensitivity to emotional stimuli on the one hand and a relatively immature cognitive control system on the other hand. However, little research has outlined to what extent relevant and irrelevant emotional stimuli bias the imbalance between affective processing and cognitive control. Thirty-three adolescents (19 females, aged 12-14) and 37 adults (18 females, aged 18-29) completed two attentional conditions of an emotional face working memory 0-back/2-back task. Participants were asked to attend to the emotional facial expression in the 'relevant' emotion condition, and to the gender of the face in the 'irrelevant' condition. The results revealed a working memory improvement for happy faces in the relevant condition in both age groups, and an impairment for irrelevant happy faces in adolescents, but not adults. Furthermore, the difference between both attentional conditions for happy faces was larger in adolescents than adults. Results are discussed within the framework of theories of adolescent behaviour.

[1] Based on Cromheeke, S., & Mueller, S.C. (in press). The power of a smile: stronger working memory effects for happy faces in adolescents compared to adults, *Cognition & Emotion,* doi: 10.1017/S0033291705005891

INTRODUCTION

Adolescence is an important transition period between childhood and adulthood during which a variety of critical physical and psychological changes take place. All of these advancements including physical growth, cognitive development, and emotional maturation result in specific patterns of motivated behaviour, leading to increased risk-taking and sensation-seeking, but also increased mortality (Dahl, 2004; Somerville, Hare, & Casey, 2011). To explain this drastic shift in behaviour, dual-process theories of adolescent development typically identify an underlying neurobiological imbalance between late maturation of prefrontal cortical regions responsible for cognitive control and a relatively early maturation of subcortical regions linked to affective processing including emotion and motivation (Ernst, Pine, & Hardin, 2006; Nelson, Leibenluft, McClure, & Pine, 2005; Somerville & Casey, 2010; Steinberg, 2008).

Within this framework, most attention has been devoted to how monetary reward improves cognitive control performance (Geier & Luna, 2009; Hardin et al., 2009; Jazbec et al., 2006; for an overview, see Richards, Plate, & Ernst, 2013), while less attention has been paid to other emotional stimuli (Mueller, 2011). The handful of studies examining such emotion-cognition interactions in adolescents have predominantly focused on the influence of emotion on inhibitory control (Hardin et al., 2009; Hare et al., 2008; Tottenham, Hare, & Casey, 2011) to explain reduced top-down control and increased risk-taking. However, previous research has shown that different cognitive control functions (e.g. inhibition, set-shifting and working memory) are separable at a theoretical (Miyake et al., 2000) and neuroanatomical level (Sylvester et al., 2003), develop at different rates (Luna, Garver, Urban, Lazar, & Sweeney, 2004), and may have a different sensitivity to emotional material (De Houwer & Tibboel, 2010; Hardin et al., 2009; Levens & Gotlib, 2010; Levens & Phelps, 2008). Thus findings in one cognitive control skill (inhibition) may not necessarily extend to other cognitive control skills (e.g., set shifting and working memory) thus precluding a generalization of findings of cognitive control skills.

Working memory (WM) is the ability to maintain and manipulate information over a short time period. Interestingly, performance on WM tasks improves throughout adolescence and only reaches an adult-like level at 19 years – compared to 14 years for

inhibition (Luna et al., 2004). Consequently, the impact of emotion on this executive function might be stronger than for cognitive skills maturing earlier. However, only limited research has been conducted in this domain. WM is frequently assessed using an n-back task, in which participants see a sequence of stimuli and are asked to indicate whether the current stimulus matches the one shown n-steps back. An emotional variant of the n-back task has already been used in adolescents and showed that healthy adolescents were more easily distracted by positive backgrounds, resulting in impaired WM performance (Ladouceur et al., 2005; Ladouceur et al., 2009). Whereas the emotional stimuli in this task were merely incidental to the main task and only served as distractors, studies in adults have used emotional n-back tasks where emotion is relevant, in order to explore how affective information is maintained and updated in WM. Results have shown that the tendency to keep negative information active in WM is exacerbated in people who suffer from depression (Levens & Gotlib, 2010), while the tendency to maintain positive information in WM is related to higher levels of psychological well-being (Pe, Koval, & Kuppens, 2013). Thus, investigating how emotional information is stored in WM in adolescents can increase our understanding of affective development during this critical period. However, no study to date has investigated differences in updating affective information in WM in adolescents compared to adults.

In the current study, we use an emotional face n-back task to address this gap in the literature. Furthermore, we explicitly manipulate the relevance of the emotional information to compare the effects of task-relevant versus task-irrelevant emotional information. Since affective stimuli are thought to attract more attention and thus require more processing resources (Pessoa, 2009), it has been argued that their impact on performance depends on the relevance of these stimuli (Kanske, 2012). This hypothesis is further supported at the neurobiological level in which task irrelevant stimuli elicit more activation than task relevant stimuli in dorsolateral prefrontal cortex and inferior parietal cortex suggesting top-down regulatory control to counteract distraction (Cromheeke & Mueller, 2014). In contexts where emotional stimuli are relevant, their preferential processing will have beneficial effects on performance such as leading to faster reaction times or reduced error rates. However, in contexts where

the affective value of stimuli is incidental, performance is impaired due to decreased processing of task-relevant content in favor of processing biologically-salient irrelevant emotional information.

Thus, this study investigated how emotional relevance impacts developmental differences in updating emotional stimuli in WM. Based on previous tasks used in adults (Levens & Gotlib, 2010; Neta & Whalen, 2011), in the current investigation adolescents (ages 12-14) and adults (ages 18-29) completed two versions of an n-back task with emotional face stimuli (happy, neutral, or angry faces). In the "irrelevant" version (the 'gender condition'), participants had to remember the gender of the face, whereas in the "relevant" version (the 'valence condition'), participants were asked to pay attention to the emotional expression. Based on adolescents' hypersensitivity to affective information as suggested by theories of adolescent behaviour (Ernst et al., 2006; Nelson et al., 2005; Somerville & Casey, 2010; Steinberg, 2008) we hypothesized to find stronger effects of emotional stimuli on WM performance in adolescents compared to adults. In the gender condition, we expected the emotional faces to be more distracting and thus impair adolescents' performance more so than adults. In the valence condition, we expected a performance improvement for the emotional faces that is more pronounced in adolescents.

METHOD

Participants

Fourty-three healthy adolescents (26 female, aged 12-14, mean age (M_{age}) = 13.5, standard deviation (SD) = 0.9) and 38 healthy young adults (19 female, aged 18-29, M_{age} = 21.0, SD = 2.6), all of Caucasian ethnicity, volunteered for this study. Adolescents were recruited in local high schools and adults were university students (mainly from the Department of Movement and Sports Sciences and the Department of Psychology and Educational Sciences) recruited via a participant website. Sample sizes were determined based on prior research using a similar emotional n-back paradigm (Levens & Gotlib, 2010). Self-report measures were used to screen for psychopathology. Adults completed the Adult Self Report (ASR; Achenbach & Rescorla, 2003), while adolescents' parents filled in the Child Behaviour Checklist (Achenbach & Rescorla,

2001). In the adolescent group, three participants were excluded because of scores in the clinical range (T>70) on the Internalizing, Externalizing or Total Problems Scale of the CBCL. An additional seven adolescents and one adult were excluded due to 2-back accuracy rates below 60%. As a result, the final sample consisted of 33 adolescents (19 female, M_{age} = 13.5, SD = 0.9) and 37 adults (18 female, M_{age} = 21.0, SD = 2.6). To control for IQ, two subtests of the Dutch WISC-III (Kort et al., 2002) or WAIS-III (Uterwijk, 2000) were administered, i.e. vocabulary and block design. Estimated IQ scores based on these two subtests have a mean reliability and validity of 0.9 (Jeyakumar, Warriner, Raval, & Ahmed, 2004; Sattler, 1992; Strauss, Sherman, Spreen, & Spreen, 2006). For exploratory reasons and to rule out psychopathology in the study sample, additional measures were also collected. These measures included the Behavioural Inhibition/Behavioural Activation System scales (BIS/BAS scales; Carver & White, 1994), the Beck Depression Inventory (BDI-II NL; Beck, Steer, Ball, & Ranieri, 1996; van der Does, 2002), the Children's Depression Inventory (CDI; Kovacs, 1992; Timbremont, Braet, & Roelofs, 2008), the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) and State-Trait Anxiety Inventory for Children (STAI-C; Bakker, van Wieringen, van der Ploeg, & Spielberger, 2004; Spielberger, 1973). The study was approved by the ethical committee of the Faculty of Psychology and Educational Sciences. Adults provided written consent and both adolescents and a parent gave written assent before participating in the study.

Stimuli

Images of 32 adult actors (16 male, 16 female) were selected from the NimStim (Tottenham et al., 2009) and Radboud Faces Database (Langner et al., 2010). To avoid overlap, for the practice trials, we used 14 faces (seven male, seven female) from the Karolinska Directed Emotional Faces database (KDEF; Lundqvist, Flykt, & Ohman, 1998). Each actor posed three emotional expressions (neutral, happy, and angry), resulting in 96 pictures. Only models with inter-participant agreement of 70% or higher (mean inter-participant agreement: 94%) for all three emotions were selected. Background and hair was removed, and images were grayscaled (256 gray levels) using Adobe Photoshop 5.0. Faces were displayed on a black background at 320x400 pixels,

corresponding to approximately 8x10cm. Based on a pilot study (n = 8), only the models consistently (> 85%) identified as male or female were included, to decrease the difficulty of the gender condition.

Procedure

Participants performed two load versions of a classic WM n-back task: a 0-back and 2-back version. Each version included two attention conditions, one in which the attention was directed to the emotional expression (the valence condition) and one where gender had to be attended to (the gender condition; see Figure 1). In the 2-back valence condition, participants compared the emotional expression of the current face with that of the face presented two trials earlier. If both expressions were the same, this was considered a match trial. If both expressions differed, it was considered a mismatch trial. In the 2-back gender condition, participants indicated whether the gender of the current face matched the gender of the face 2 trials before. Participants were asked to press the left mouse button for a match and the right mouse button for a mismatch trial. In the 0-back task participants responded to a target. In the valence condition, this target was either a happy, neutral, or angry expression. In the gender condition, the target was a male or female face. Targets were counterbalanced and had a random order within each attention condition. Participants were asked to press the left mouse button if the target was shown and the right mouse button if the stimulus was not a target.

To match the difficulty of the gender and valence condition and allow orthogonality of the factors, only two emotions were shown in each block (happy-neutral, happy-angry, or angry-neutral). Stimuli were presented for 2000 ms, with an intertrial interval of 500 ms. In the 0-back task, participants completed 12 blocks of 12 trials, each block being a different combination of emotion (happy-neutral, happy-angry or angry-neutral), attention condition (valence or gender condition) and target (one of both emotions in this block). The 2-back task consisted of six blocks containing 32 trials each (a happy-neutral, happy-angry, and angry-neutral block for each attention condition). The order of match and mismatch trials was pseudo-randomized, such that no more than four faces in a row were match trials. The order of cognitive load versions (0-back or 2-back) was counterbalanced. Within load versions, participants started

either with the valence or the gender condition and within this attention condition, they completed the emotion blocks in a random order.

Instructions were given orally first and then repeated in writing on screen. Within one block, every actor was shown only once, to avoid confusion with identity. However, between blocks the emotion that an actor expressed was randomized. Before starting the experimental trials, participants practiced the task with a different set of faces and were informed about which emotions they would see. Each practice block consisted of 10 (0-back) or 24 (2-back) trials, and participants only continued to the experimental blocks if they had an accuracy rate of at least 60%. The task was programmed using Presentation software (Neurobehavioral Systems, www.neurobs.com) and presented on a 15.6" Dell laptop running Windows 7. All participants were tested in experimental rooms at the department.

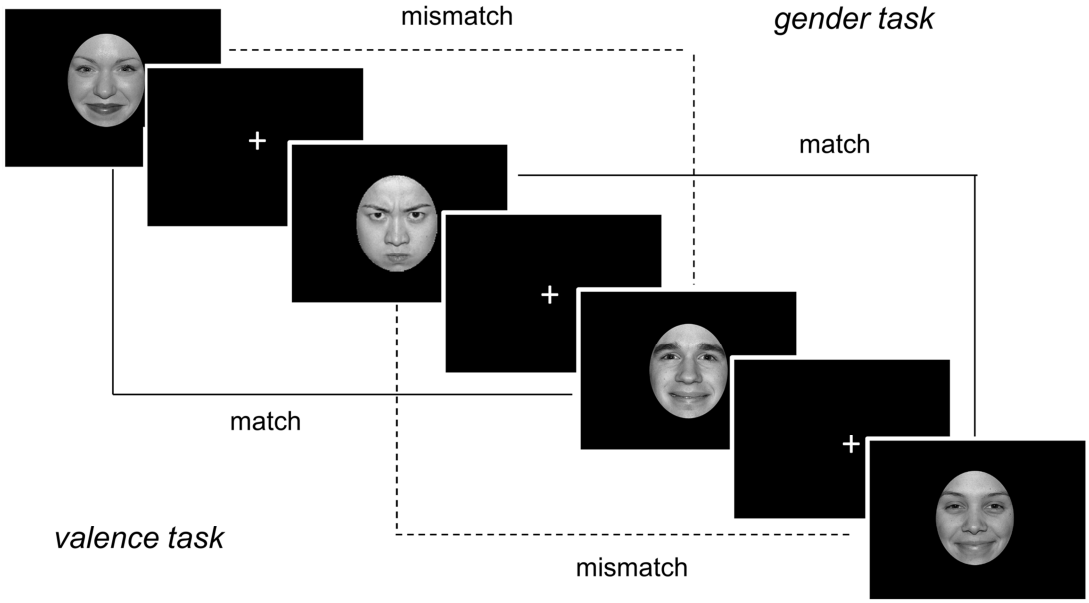

Figure 1. Experimental design of both attention conditions (gender and valence condition) in the face 2-back task. In the valence condition (left corner), match trials were trials where the emotional expression of the current face matched the one that appeared two trials earlier. In the gender condition (right corner), match trials were trials where the gender of the current face matched the gender of the face two trials back. Each face was presented for 2000 ms, followed by a fixation cross for 500 ms.

Statistical analysis

We performed a repeated measures Analysis of Covariance (ANCOVA) with Load (2 levels: 0-back vs. 2-back task), Attention condition (2 levels: gender vs. valence condition) and Emotion (3 levels: happy, angry and neutral) as within-subjects factors and Age group (2 levels: adolescents and adults) as between-subjects factor. Since groups differed on Estimated IQ, this factor was added as a covariate of no interest in the ANCOVA. To follow-up significant interactions, paired-samples t-tests were used. All p-values were corrected for multiple comparisons with a Bonferroni step-down (Holm) procedure. Alpha was set at $p = .05$, two-tailed. Measures of effect size are reported as partial η^2, Cohen's *d* or Cramer's V (as appropriate).

For the reaction time analysis, trials with incorrect responses and outliers were removed. Outliers were reaction times more than 3 standard deviations from the individual mean reaction time for 0-back and 2-back separately (Howell, 2002; 0.01% of the data).

Given the trending between-group differences on STAI(C)-Trait and Total BAS, we explored whether these might influence our conclusions by adding them as covariates in an additional analysis. Since all effects remained significant, the results of this analysis are not further discussed.

RESULTS

Participant characteristics

Demographic information and mean estimated IQ scores are shown in Table 1. The reported IQ score is a composite of the scaled scores of the two subtests from the Dutch WISC-III or WAIS-III. Results indicated a significant Age group effect of IQ, $t(68) = 3.86$, $p < .001$, partial $\eta^2 = .18$. Therefore, IQ was included as a covariate of no interest in between-group analyses. No significant differences were found for Total score on the ASR/CBCL, $t(67) = 1.14$, $p = .260$, partial $\eta^2 = .019$.

Table 1. Demographic information and mean scores (SD) for the questionnaires and Estimated IQ results in the adolescent and adult group

Variable	Adolescents (N = 33)	Adults (N = 37)	p-value	Effect size
Age	13.5 (0.92)	21.0 (2.60)	-	-
Female (N)	19	18	.455[a]	.089[c]
Total ASR/CBCL	45.56 (8.96)	47.76 (6.89)	.260[b]	.019[d]
Estimated IQ	21.24 (3.80)	24.49 (3.16)	< .001[b]	.180[d]
Total BIS	20.21 (3.66)	20.78 (3.00)	.475[b]	.008[d]
Total BAS	38.42 (4.77)	40.57 (4.84)	.067[b]	.049[d]
CDI/BDI	-.28 (1.12)	-.15 (.77)	.554[b]	.005[d]
STAI(C)-Trait	.14 (1.02)	-.29 (.86)	.061[b]	.051[d]
STAI(C)- State	-.20 (.84)	-.35 (.82)	.466[b]	.008[d]

T-scores are used for Total ASR/CBCL; Raw scores are presented for Total BIS and Total BAS; z-scores are reported for CDI/BDI, STAI(C)-Trait and STAI(C)-State; Norm scores are used for WISC/WAIS results

[a] chi-square, [b]two-sided t-test for independent samples, [c]Cramer's V, [d]partial η^2

Reaction time

The reaction time (RT) analysis yielded a significant three-way Attention condition by Emotion by Age group interaction, $F(2, 134) = 3.63$, $p = .029$, partial $\eta^2 = .05$. There was also a main effect of Load, $F(1,67) = 13.16$, $p = .001$, partial $\eta^2 = .16$, indicating faster RTs on the 0-back compared to the 2-back task, and a main effect of Age group, $F(1, 67) = 10.06$, $p = .002$, partial $\eta^2 = .13$, with adolescents responding slower than adults. The four-way interaction of Attention condition, Load, Emotion and Age group was not significant, $F(2, 134) = 1.70$, $p = .19$, partial $\eta^2 = .03$. To understand the significant three-way interaction, an Attention condition by Emotion ANOVA was run for adolescents and adults, separately (see Figure 2).

The Attention condition by Emotion interaction was significant in adolescents, $F(2,64) = 15.28$, $p < .001$, partial $\eta^2 = .32$, and the main effect of Emotion was also significant, $F(2, 64) = 4.43$, $p = .016$, partial $\eta^2 = .12$. Paired samples t-tests were used to follow up significant differences within Emotion condition and between Attention

conditions. RTs for happy faces were significantly faster in the valence than in the gender condition, t(32) = 4.55, p < .001, *d* = 0.56, while no differences were found for angry, t(32) = 0.07, p = .95, *d* = 0.01, and neutral faces, t(32) = -1.10, p = .56, *d* = .12. Additionally, RTs within Attention condition also differed significantly, with faster RTs for happy faces compared to neutral, t(32) = -5.25, p < .001, *d* = 0.44, and angry faces in the valence condition, t(32) = 5.62, p < .001, *d* = 0.41, and slower RTs for happy compared to neutral faces, t(32) = 2.76, p = .04, *d* = .20, in the gender condition.

In adults, Attention condition also interacted significantly with Emotion, F(2,72) = 3.97, p = .023, partial η^2 = .10, and there was a main effect of Emotion, F(2, 72) = 5.79, p = .005, partial η^2 = .14. Contrary to the findings in adolescents, paired samples t-tests indicated no significant RT differences between Attention conditions for either happy, t(36) = 1.55, p = .35, *d* = 0.15 , angry, t(36) = -.31, p = .74, *d* = 0.03, or neutral faces, t(36) = -1.62, p = .35, *d* = 0.17 (Figure 2). Analyses within attention conditions indicated faster RTs for happy faces compared to neutral, t(36) = -4.27, p < .001, *d* = 0.36, and angry, t(36) = 3.51, p = .006, *d* = 0.33, faces in the valence condition, similar to what was found in adolescents. However, no differences were found in the gender condition, all p-values > .49.

To further assess whether the difference for happy faces varied significantly between adolescents and adults, both within and between Attention conditions, a one-way Analysis of Variance was performed on RT difference scores. The difference score between Attention conditions ([RT for happy faces in the gender condition – RT for happy faces in the valence condition]) was larger in adolescents than adults, F(1, 68) = 9.12, p = .004, partial η^2 = .12. To examine whether the WM improvement in the valence condition differed between age groups, we calculated a difference score for happy compared to neutral faces. Even though this score was also larger in adolescents than adults, this difference was not significant, F(1, 68) = 2.04, p = .158, partial η^2 = .03.

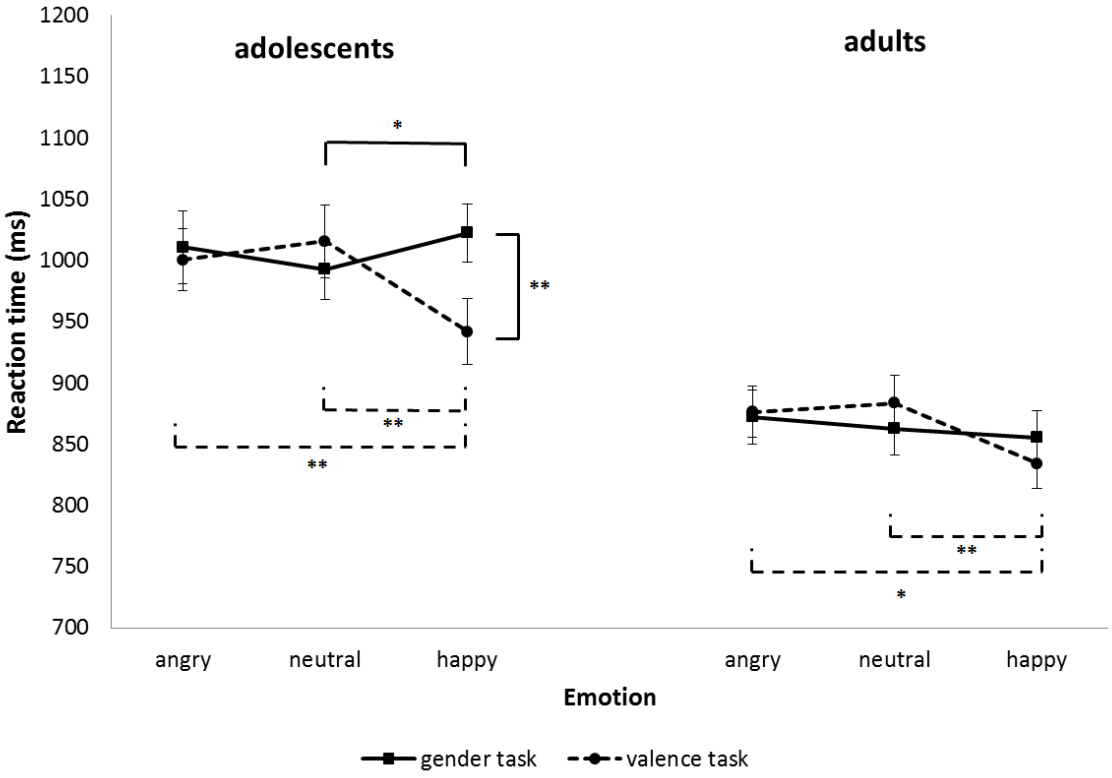

Figure 2. RTs (ms) for adolescents (left panel) and adults (right panel), split by emotional valence of the stimuli. Error bars denote standard error of the mean. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). The vertical bar indicates the significant effect for happy faces between tasks in adolescents. The horizontal bars indicate the significant effect within the valence condition (dotted line) and within the gender condition (full line).

Accuracy

In the accuracy data, a main effect of Load, $F(1, 67) = 30.17$, $p < .001$, partial $\eta^2 = .31$, indicated higher accuracy scores for the 0-back (92.4%) compared to the 2-back task (76.3%). A main effect of Age group, $F(1, 67) = 14.49$, $p < .001$, partial $\eta^2 = .18$, revealed higher accuracies for adults (86.5%) than for adolescents (82.3%). There was also a significant Load by IQ interaction, $F(1, 67) = 9.30$, $p = .003$, partial $\eta^2 = .12$. IQ correlated significantly positively with accuracy on the 2-back, $r(70) = .49$, $p < .001$, but not on the 0-back task, $r(70) = .13$, $p = .29$. The main effects of Attention condition and Emotion were not significant, $F(1,67) = .02$, $p = .90$, partial $\eta^2 < .001$ and $F(2, 134) = .49$, $p = .62$, partial $\eta^2 = .007$, respectively, as were all other interactions (all $p > .16$). An overview of the accuracy and RT data can be found in Table 2.

Table 2. Reaction times (mean and SD, in ms) and accuracy rates (mean and SD, in %) for adolescents and adults

A. 0-back task

		Adolescents				Adults			
		RT		Acc		RT		Acc	
Attention condition	Emotion	M	SD	M	SD	M	SD	M	SD
Gender task	Angry	861	162	88	9	728	120	92	7
	Happy	862	124	92	10	696	113	94	7
	Neutral	860	140	92	6	697	98	93	8
Valence task	Angry	856	141	88	9	691	116	93	7
	Happy	801	157	93	7	672	94	96	4
	Neutral	889	162	91	9	726	122	96	5

B. 2-back task

		Adolescents				Adults			
		RT		Acc		RT		Acc	
Attention condition	Emotion	M	SD	M	SD	M	SD	M	SD
Gender task	Angry	1158	197	73	10	1027	171	78	12
	Happy	1193	184	75	7	1025	186	83	11
	Neutral	1138	186	73	8	1034	212	80	10
Valence task	Angry	1161	187	70	9	1073	195	78	12
	Happy	1095	187	75	13	1014	192	82	12
	Neutral	1148	216	70	12	1052	208	79	12

Correlational analyses

To assess whether differences on the task related to symptoms of depression, anxiety and approach/avoidance behaviour, a correlational analyses was carried out between questionnaire scores and task performance. However, correlations between the BDI/CDI z-score, STAI Trait z-score, Total BIS and Total BAS on the one hand and difference scores between happy and neutral faces and between angry and neutral faces in both attention conditions separately on the other hand were not significant (all $p > .17$).

DISCUSSION

This study assessed how relevance of an emotional stimulus modulated its influence on interfering with working memory (WM) during development. We hypothesized a WM improvement for relevant and impaired WM for irrelevant emotional stimuli in both age groups but, given a proposed hypersensitivity to emotional stimuli during adolescence, we hypothesized the effects to be larger in adolescents relative to adults. In line with our initial hypothesis, allocating attention to affective information improved WM in both age groups, although this effect was specific to happy faces. However, if attention was allocated to non-emotional information (i.e. gender), adolescents were slower for happy compared to neutral faces, while adult performance was not sensitive to emotion in this condition.

The beneficial effect of task-relevant happy faces on WM is in-line with previous research reporting a bias towards positive emotional stimuli in healthy individuals (Levens & Gotlib, 2010; Pe et al., 2013). Using a similar emotional n-back task, Levens and Gotlib (2010) found that healthy adults were better at updating positive information in WM and took longer to disengage from happy faces. The current study not only extends this finding to healthy adolescents but also clearly indicates that this effect depends on specific task demands. Interestingly, when attention was directed to non-affective features of the faces, making the expression irrelevant to the task goal, working memory performance was no longer modulated by the valence of the face in

adults. However, adolescents' performance was impaired for happy compared to neutral faces in this condition. Thus, the affective information might have distracted adolescents, 'hijacking' attentional processing resources from the actual task. For instance, Ladouceur et al. (2005) suggested that attentional capture of salient positive stimuli might underlie such pulling of attentional resources. In her study, healthy adolescents had slower reaction times on a WM task when the target stimuli were presented on a positive compared to a neutral background picture during 0-back and 2-back conditions. Our findings are in-line with such a notion.

In fact, the difference for happy faces between both attention conditions in adolescents is also consistent with theories on adolescent development proposing hypersensitivity to emotional – especially positive – stimuli in this age cohort (Ernst et al., 2006; Hardin et al., 2009; Nelson et al., 2005; Somerville & Casey, 2010; Steinberg, 2008). Interestingly, this hypersensitivity has been associated with increased activation in the ventral striatum (Ernst et al., 2006), a region associated with reward processing. This structure has also been found to be more active in adolescents in response to pictures of happy faces (Pfeifer et al., 2011; Somerville et al., 2011), suggesting that these stimuli might serve as a social reward. Indeed, previous studies found that happy faces can serve as an incentive in 10 year old children (Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009) and adults (Spreckelmeyer et al., 2009).

The finding that happy faces affect performance more in adolescents than adults could be due to increased saliency (or 'chronic relevance', see Eitam et al., 2014; Eitam & Higgins, 2010) of these biologically relevant stimuli. While both age groups are sensitive to social cues, adolescence is characterized by increased reliance on, and importance of, social signals, especially feedback from peers (Guyer, Choate, Pine, & Nelson, 2012; Jones et al., 2011; Somerville, 2013). A propensity for approaching these positive stimuli might help adolescents to fulfill tasks that are associated with this developmental period, i.e. starting an independent life. Therefore, in our study adolescents' attention might have been more easily captured by happy faces, hindering the processing of other stimulus features (i.e. the gender of the face). Given the tight interplay between attentional and working memory processes (Gazzaley & Nobre, 2012), this attentional capture (Ladouceur et al., 2005) could have resulted in impaired performance on the gender n-back task, while improving performance if the emotional

valence was the relevant dimension and became the center of focus. An alternative explanation for the specificity of these effects for happy faces could be that these stimuli are often considered more physically attractive and rewarding than if the same person is shown with an angry or neutral expression (Kampe, Frith, Dolan, & Frith, 2001; O'Doherty, Critchley, Deichmann, & Dolan, 2003). Future research could disentangle the effect of valence and attractiveness by comparing performance for physically attractive and non-attractive happy faces, and by using other positive expressions such as pride or joy.

Somewhat surprisingly, the reaction time difference between positive and neutral stimuli seemed to be independent of load. Yet, this is consistent with previous studies in healthy adults showing better performance for happy compared to neutral faces both on a 0-back task as well as on a 2-back task (Levens & Gotlib, 2010, 2012), whereas findings in adolescents have been mixed with regard to the effect of load (Ladouceur et al., 2005; Ladouceur et al., 2009). The increased sensitivity to happy faces in adolescents reported in the current study could indicate a more general effect that is not restricted to working memory per se but may additionally involve low level attentional processes given that there was no significant interaction with load. Given the ambivalence in findings between adolescents and adults, however, independent replication is needed. For example, future work could examine the exact role of cognitive load in emotional working memory tasks by including more levels of cognitive load (e.g. 1-back and 3-back). Neuroimaging studies could also shed some light on this issue by investigating whether activity in affective regions remains high or is down-regulated when cognitive load is increased (i.e. during a 2-back task compared to a 0-back task).

In contrast to the performance improvement for happy faces and contrary to our expectations, angry faces did not influence latencies in either the relevant or irrelevant version of the emotional n-back task. Based on dual-process theories positing increased sensitivity to emotional stimuli in adolescence (Nelson et al., 2005; Somerville & Casey, 2010; Steinberg, 2008), we predicted improved performance for relevant emotional stimuli and impaired performance for irrelevant emotional stimuli. However, results indicated differential valence effects, with positive stimuli improving or

impairing performance depending on the relevance of emotional information, whereas negative stimuli had no effect. Even though the absence of an effect for negative stimuli is not consistent with our hypothesis, this finding is not surprising given previous research on emotional influences on WM. For example, in the n-back task with distracting emotional backgrounds mentioned earlier, Ladouceur et al. (2005) found an effect of positive backgrounds in healthy adolescents, while impaired performance for negative backgrounds was only found in adolescents with affective disorders. Similar findings have been reported, both in adults (Levens & Gotlib, 2010) as well as in children (Visu-Petra, Tincas, Cheie, & Benga, 2010). Using a WM updating task, Visu-Petra et al. (2010) found a bias towards happy faces in low anxious and towards angry faces in high anxious children. In adults, positive bias has been found in healthy adults, whereas depressed adults seem to be biased towards negative stimuli (Levens & Gotlib, 2010).

Given that the emotional face n-back task has often been used in the context of research on mood and anxiety disorders (for review see Mueller, 2011), our findings in healthy participants might also bear implications for theories of psychopathology in adolescence. On the one hand, some studies have reported a bias towards positive information in healthy individuals (Hardin et al., 2009) thus improving performance. On the other hand, depressed adolescents (Ladouceur et al., 2005) and adults (Levens & Gotlib, 2010) show a bias towards negative stimuli, while young adults with history of childhood maltreatment show impairments during positive stimuli in working memory tasks (Cromheeke, Herpoel, & Mueller, 2014). These data suggest that sensitivity to positive information might constitute a protective factor against depression in healthy individuals or a risk factor for psychopathology in vulnerable groups. Indeed, recent studies have demonstrated an association between a positivity bias during a WM task and both well-being (Pe et al., 2013) and optimism (Levens & Gotlib, 2012). In the current study, exploratory correlational analyses were carried out to examine the relationship between performance on the emotional working memory task and depressive and anxiety symptoms, but no significant correlations were found. Of course, only healthy individuals were included in this study thus limiting the variance in levels of symptoms. Therefore, future studies should investigate WM bias for emotional

information in depressed adolescents to gain more insight into the development of this disorder.

One limitation of this study, which is also a strength, concerns the narrow age range of both groups. Even though adolescence can be roughly defined as the period between 10 and 20 years of age, in this study we only included 12-14-year old participants. This limited inclusion criterion was chosen to avoid any overlap in developmental stage between both groups and to limit the inter-individual variability within the adolescent group. As a result, although our findings are in line with theories of adolescent development, it is unclear whether our effects are specific to adolescents or whether they would extend to other developmental periods as well. Future studies are needed to generalize our findings to younger and older cohorts and to examine the interaction between emotion and cognitive development across the entire developmental period.

Conclusion

In summary, the present study tested to what extent relevant vs. irrelevant emotional information impacted WM performance in adults and adolescents. Presence of happy faces improved performance in both groups if they were relevant to the task. In contrast, if emotional valence was incidental, performance for happy faces was impaired in adolescents but not in adults. These findings are in line with theories of adolescent behaviour proposing hypersensitivity to positive stimuli during adolescence (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008). Future work should examine the neural underpinnings of these findings to gain more insight into the integration of social rewards and cognitive control in the adolescent brain (Blakemore, 2008; Steinberg, 2008).

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CHAPTER 4

NEURAL CORRELATES OF WORKING MEMORY FOR (IR)RELEVANT EMOTIONAL STIMULI: A COMPARISON BETWEEN ADOLESCENTS AND ADULTS

ABSTRACT

Previous evidence has indicated that emotional and cognitive brain regions develop at different rates during adolescence. Neurobiological theories have proposed that this lag of cognitive control development combined with a hypersensitive emotional system could explain the increased risk-taking and heightened prevalence of depression in this age period (Ernst, Pine, & Hardin, 2006; Somerville & Casey, 2010; Steinberg, 2008). In a previous study (Chapter 3), we investigated the interaction between emotional and cognitive control processes using an emotional face 0-/2-back task. Results indicated a working memory improvement in both adolescents and adults for happy faces when they were asked to remember the emotional expression (*valence task*). However, when attention had to be directed to a non-emotional feature, i.e. the gender of the face (*gender task*), only adolescents showed an impairment when presented with happy faces. In the current study, we administered the same task in both age groups while they were undergoing functional magnetic resonance imaging (fMRI). Results showed that adolescents under-recruited a range of fronto-parietal regions. Interestingly, activity in the left inferior frontal gyrus and right dorsolateral prefrontal cortex was sensitive to the emotional manipulation in adults, but not adolescents. Furthermore, developmental differences were also found in bilateral amygdala, with adolescents generally showing higher activation compared to adults.

INTRODUCTION

In a previous behavioural study (see Chapter 3), we have compared the performance of adolescents and adults on a task measuring working memory for relevant and irrelevant emotional content. More specifically, we administered two attentional conditions of a 0-back/2-back task with happy, angry and neutral face stimuli. In the 'irrelevant' condition, participants were asked to neglect the emotional information and focus on the gender of the face (*gender task*). In the 'relevant' condition, on the other hand, they were asked to remember the valence of the face (*valence task*). Results indicated a working memory improvement, i.e. faster reaction times (RTs), for relevant happy faces in adolescents and adults. In the gender task, however, only adolescents showed an effect of the emotional manipulation, with slower RTs for irrelevant happy compared to neutral faces. These results fit with neurobiological theories of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), positing an imbalance between emotional and cognitive processing during adolescence. Research has indicated that, when confronted with affective information, adolescents show heightened activity in subcortical emotional regions such as the amygdala and ventral striatum (Galvan et al., 2006; Guyer, Lau, et al., 2008; Monk et al., 2003). At the same time, this age period is characterized by immature prefrontal functioning, especially in emotional contexts (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Hare et al., 2008). The combination of this enhanced emotional reactivity in subcortical regions and underdeveloped top-down prefrontal system has been suggested to underlie the increase in risk-taking behaviour and the rising incidence of affective disorders during adolescence. Thus, when confronted with affective stimuli, adolescents are thought to exhibit less efficient top-down prefrontal control over hyperactive emotional regions, leading to poor emotion regulation and increasing the chance of developing an affective disorder.

In the behavioural study reported in Chapter 3, only working memory for positive stimuli differed between adolescents and adults, while no developmental differences were detected for negative stimuli. The goal of the current study is to examine how these findings are related to differences in brain activation. To this aim, adolescents and adults performed the same emotional n-back task while undergoing

functional magnetic resonance imaging (fMRI). In the analysis, we specifically focused on the regions of interest that were identified in the meta-analysis described in Chapter 2 (Cromheeke & Mueller, 2014). In that study, we reviewed research reporting neurological correlates of experimental tasks integrating cognitive control and affective processing in adults. Using the activation likelihood estimation (ALE) meta-analysis method (Eickhoff et al., 2009; Turkeltaub, Eden, Jones, & Zeffiro, 2002), we summarized these findings and showed that within a cognitive control context, emotional compared to neutral stimuli consistently activated a range of brain regions. These included both regions traditionally involved in cognitive control, such as the lateral prefrontal cortex, the medial prefrontal cortex, and the basal ganglia, as well as regions that are viewed as 'emotional', such as the amygdala. Interestingly, activation in these regions also differed depending on the relevance of the emotional stimuli within the cognitive control task. If processing the valence of the emotional stimuli was not necessary to correctly perform the task, thus making the emotion irrelevant, activation in the right dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL) was increased.

The current study is aimed at identifying developmental differences in these regions while participants perform a task combining emotional and cognitive processing, i.e. the emotional face n-back task. Given an imbalance between prefrontal and emotional regions in adolescents (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), we expected to find hyperactivation of the limbic circuitry (e.g. amygdala and ventral striatum) and decreased activity in prefrontal regions responsible for cognitive control (e.g. dorsolateral prefrontal cortex, inferior frontal gyrus and medial frontal gyrus).

METHOD

Participants

Fourty-five healthy adolescents (25 female) aged 12-16 years and 32 healthy adults (17 female) aged 25-35 years volunteered to participate in the study. All participants were native Dutch speakers and had normal or corrected-to-normal vision. The study was approved by the Ethical Committee of the Ghent University Hospital. An

informed consent form was obtained from each participant, and for the adolescent group also from a parent. Magnetic resonance imaging (MRI) exclusion criteria included a history of neurological illness (e.g. epilepsy), a positive pregnancy test and metal in the body.

Adults filled in the Beck Depression Inventory and the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970), while adolescents completed the Children's Depression Inventory (CDI; Kovacs, 1992; Timbremont, Braet, & Roelofs, 2008) and the State-Trait Anxiety Inventory for Children (STAI-C; Bakker, van Wieringen, van der Ploeg, & Spielberger, 2004; Spielberger, 1973). Additionally, they also completed the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988). The Behavioural Inhibition/Behavioural Activation System scales (BIS/BAS scales; Carver & White, 1994) and the Edinburgh Handedness Inventory were administered in both adolescents and adults. IQ was assessed using the subtests 'Vocabulary' and 'Block Design' of the Dutch Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2012) and the Wechsler Intelligence Scale for Children (WISC-III; Kort et al., 2002). To rule out the presence of internalizing or externalizing disorders, adults filled in the Adult Self Report (ASR; Achenbach & Rescorla, 2003), while adolescents' parents completed the Child Behaviour Checklist (CBCL; Achenbach & Rescorla, 2001). Participants with a clinical score on the ASR (n = 2) or CBCL (n = 3) or a z-score higher than 2 on the STAI, STAI-C (n = 2), BDI or CDI (n = 3) were excluded from the analysis. Additional exclusion criteria were excessive (> 4mm) head movement in the scanner (n = 10) and an accuracy score on the 2-back task lower than 60% (n = 2). Furthermore, fMRI data from two participants was incomplete and could not be included in the analysis. As a result, the final sample included 24 adolescents (16 female; M_{age} = 14.5; SD_{age} = 1.24) and 28 adults (14 female; M_{age} = 27.49, SD_{age} = 2.11).

Experimental paradigm

The emotional n-back task was the same as in the behavioural study described in Chapter 3, with the following changes that were necessary for adapting it to the MRI environment: 1) the duration of the inter-trial interval was jittered between 300 and 700 ms, to ensure that the length of a trial would be different from the repetition time (TR), 2) the experimental task consisted of two runs, one for each cognitive load version

(0-back and 2-back), and 3) after each block in the 0-back task, participants received a 15s break and after each 2-back block this break lasted 60s. Participants heard a sound indicating the start of a new block, to ensure they were focusing on the task again.

The number of trials was the same as reported in Chapter 3. The 0-back task consisted of 12 blocks of 12 trials, while the 2-back task included six blocks of 32 trials. In half of the blocks, participants were asked to focus on the valence of the expression that was shown (*valence task*), and in the other half they were asked to focus on the gender of the face (*gender task*). Given that the gender task only included two response options (male or female), the faces that were shown in each block were also limited to two emotional expressions. In the 0-back task, each combination of attention condition (valence or gender task) and emotion (happy-neutral, angry-neutral or happy-angry) was shown twice, with the target being male or female (in the gender task) or one of the two emotions in that block (in the valence task).

Prior to scanning, all participants received information about the scanning procedure. A mock scanner was used to familiarize participants with the scanner environment. They were asked to lie down in the mock scanner, listen to prerecorded sounds of the MRI sequences (SimFX, Psychology Software Tools Inc) and practice lying still using a head motion tracker (MoTrak Software, Psychology Software Tools Inc). Participants also practiced the experimental task outside the scanner to get acquainted with the task and to ensure an accuracy rate of at least 60% on both the 0-back and 2-back task.

fMRI data acquisition

All fMRI data were collected on a 3T Siemens Trio MR scanner at the Ghent University Hospital. A high-resolution structural image was acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence (flip angle = 9°; field of view (FOV) = 256mm; repetition time (TR) = 2250ms; echo time (TE) = 4.18ms). Functional images were obtained with a gradient-echo echo planar imaging (EPI) sequence (TE = 35ms; TR = 2500ms; FOV = 192mm; flip angle = 80°; voxel size = 3 x 3 x 3 mm), with each volume consisting of 36 interleaved 3mm thick slices, AC-PC aligned.

Behavioural data analyses

Reaction times and accuracy scores were acquired while participants performed the task in the scanner. These data were analyzed using a repeated-measures analysis of variance (ANOVA) with Age group as between-subjects factor and Load, Attention condition and Emotion as within-subjects factors. Significant effects were followed up with additional ANOVA's or paired-samples t-tests, as appropriate. All p-values were Holm-corrected for multiple comparisons. Reaction time analyses were restricted to correct trials only. Furthermore, RT's more than 3 standard deviations away from the individual mean RT for the 0-back and 2-back separately were excluded from the analysis (0.01% of the data; Howell, 2002). To check if performance was related to psychopathology or personality characteristics, exploratory correlational analyses were conducted between accuracy/reaction times and estimated IQ, CDI/BDI z-score, Total BIS, Total BAS, STAI Trait z-score and, for adolescents, PDS score.

fMRI data preprocessing

The fMRI data were preprocessed and analyzed with Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) in a Matlab Environment (Mathworks, Sherborn, MA). On each functional run, the first four scans were discarded to ensure steady-state magnetization. The experimental task started after the 5^{th} scanner pulse. All images were reoriented along the AC-PC line. Functional images were slice time corrected, realigned to the first acquired EPI and co-registered to the anatomical T1-image, which was normalized into a standard stereotactic space (Montreal Neurological institute, MNI). Then, EPIs were also normalized into MNI space and spatially smoothed using an 8-mm full width at half-maximum (FWHM) Gaussian kernel. A high-pass filter of 128s was used.

fMRI data analysis

Regions of interest analysis

At the first level, the BOLD responses were convolved using a canonical hemodynamic response function (HRF) and entered into general linear model (GLM; Friston et al., 1994). This model included all conditions (Load x Attention condition x

Emotion) as regressors of interest. Incorrect trials for each run (0-back and 2-back) were modeled as separate regressors of no-interest. Furthermore, the model also incorporated six movement parameters derived from the realignment and a general mean for each run. Individual whole brain statistical maps were constructed for all conditions relative to baseline. On the second level, we conducted a regions of interest (ROI) analysis to examine activation in the regions identified in the meta-analysis described in Chapter 2. In this ALE meta-analysis, we identified regions that were activated during high versus low load cognitive control when emotional (versus neutral) stimuli were presented or within an emotional/reward context. All ROIs are listed in Table 3. ROIs were created with the MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002) and defined as 10mm spheres centered around the peak coordinates from the interaction analysis (cf. Table 2 in Chapter 2). Additional ROIs consisted of left and right amygdala and ventral striatum, since these regions are central to neurobiological theories of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008). These ROI masks were created using the WFU PickAtlas (Wake Forest University, USA; Maldjian, Laurienti, Kraft, & Burdette, 2003) and Anatomical Automatic Labeling (AAL; Tzourio-Mazoyer et al., 2002) toolboxes. The MarsBaR toolbox was used within SPM8 to extract mean activation estimates (beta weights) from the ROIs for each condition. The beta weights were then examined statistically using a repeated measures analysis of variance (ANOVA) in SPSS 18 (SPSS Inc, Chicago, USA) with Group as between-subjects factor and Load, Attention condition and Emotion as within-subjects factors. We applied a Bonferroni correction to correct for multiple ROIs for the effects of Load, Attention condition and Emotion. Since we were specifically interested in the differences between groups, a more lenient threshold of $p < .05$, uncorrected for the number of ROIs, was used for main effects and interaction effects with Group.

Exploratory whole brain analyses

For the whole brain analysis, first level contrasts for all conditions relative to baseline were entered into a second level random effects flexible factorial model, using the GLM Flex Fast 2 toolbox (developed by Aaron Schultz, Martinos Center for Biomedical Imaging) in Matlab (Mathworks, Sherborn, MA), with Subjects as random

factor, Group as between-subjects factor and Load, Attention condition and Emotion as within-subjects factors. To correct for multiple comparisons, we used a mixed approach combining both voxel-wise and cluster-wise thresholds. Monte Carlo simulations (N = 1000) were performed on the whole-brain mask to determine the appropriate cluster-wise statistical threshold. Clusters were considered significant if they exceeded a voxel-wise threshold of $p < .001$ and a cluster size of 21 contiguous voxels.

fMRI correlational analyses

To facilitate interpretation of activation differences in adults and adolescents, parameter estimates in all ROIs were correlated with performance (i.e. RT and accuracy), Estimated IQ scores and questionnaire measures (Total BIS, Total BAS, CDI/BDI z-scores, STAI-Trait z-scores and, for adolescents, PDS score). This was done for the 0-back and 2-back task separately, and for the task as a whole. To correct for multiple comparisons across all ROIs, we adopted a false discovery rate (FDR) of $p < .05$ (Benjamini & Hochberg, 1995). For the correlational analysis following up significant effects in the ROI analysis, a step-down Holm correction was applied.

RESULTS

Participant characteristics

Demographic information and results of the questionnaire measures can be found in Table 1. Estimated IQ is the sum of the scaled scores of the 'Vocabulary' and 'Block Design' subtests from the Dutch WAIS-III or WISC-III, multiplied by five, to obtain a score that is comparable to a full scale IQ score. Although total scores on the CBCL/ASR differed significantly, these scores were not considered further, given that these questionnaires were only designed for screening purposes, leading to a relatively high number of false positives and false negatives. Participants also differed on handedness, with more left-handed/ambi-dextrous participants in the adolescent group. To control for these differences, an additional ROI analysis was carried out with handedness as covariate of no interest in brain regions indicating group differences. Other measures were not significantly different between groups.

Table 1. Demographic information and mean scores (SD) for the questionnaires and Estimated IQ results in the adolescent and adult group

Variable	Adolescents (N = 24)	Adults (N = 28)	p-value	Effect size
Age	14.5 (1.24)	27.49 (2.11)	-	-
Female (N)	16	14	.23[a]	.17[c]
Total ASR/CBCL	39.75 (11.09)	46.43 (7.37)	.01	.12
Estimated IQ	109.58 (16.08)	116.61 (20.37)	.18[b]	.04[d]
Total BIS	19.79 (4.41)	20.86 (3.17)	.32[b]	.02[d]
Total BAS	39.54 (4.03)	40.25 (4.08)	.53[b]	.01[d]
Handedness (A/L/R[e])	6/3/15	2/0/26	.02[b]	.39[d]
CDI/BDI	-.22 (1.23)	-.44 (.59)	.40[b]	.02[d]
STAI(C)-Trait	-.03 (.96)	-.50 (.81)	.06[b]	.07[d]

T-scores are used for Total ASR/CBCL; Raw scores are presented for Total BIS and Total BAS; z-scores are reported for CDI/BDI and STAI(C)-Trait; Estimated IQ results are extrapolated from the sum of the two subtest scores

[a] chi-square; [b]two-sided t-test for independent samples; [c]Cramer's V; [d]partial η^2

[e]A = ambidexterous; L = left-handed; R = right-handed

Reaction time

Reaction times on the 0-back task were faster than on the 2-back, $F(1, 50) = 170.68$, $p < .001$, partial $\eta^2 = .77$. There was also a significant interaction between Load and Group, $F(1, 50) = 19.67$, $p < .001$, partial $\eta^2 = .28$, indicating faster RTs for adults compared to adolescents on the 0-back task, $F(1, 50) = 11.50$, $p = .001$, partial $\eta^2 = .19$, but not on the 2-back task, $F(1, 50) = .62$, $p = .44$, partial $\eta^2 = .01$.

Furthermore, there was a significant main effect of Emotion, $F(2, 100) = 28.45$, $p < .001$, partial $\eta^2 = .36$, and Emotion interacted significantly with Attention condition, $F(2, 100) = 9.89$, $p < .001$, partial $\eta^2 = .17$. In the gender task, there was a significant main effect of emotion, $F(2, 100) = 5.72$, $p = .004$, partial $\eta^2 = .10$, indicating slower RTs for angry compared to happy ($p = .008$) and neutral faces ($p = .04$). In the valence task, the main effect of emotion was also significant, $F(2, 100) = 31.88$, $p < .001$, partial $\eta^2 =$

.39, and follow-up tests showed faster RTs for happy compared to angry ($p < .001$) and neutral faces ($p < .001$) and slower RT's for angry compared to neutral faces ($p = .01$). As can be seen in Figure 1, a difference between the valence and gender task was found for happy, $t(51) = 3.52$, $p = .002$, but not for angry, $t(51) = -.74$, $p = .62$, or neutral faces, $t(51) = -1.02$, $p = .62$.

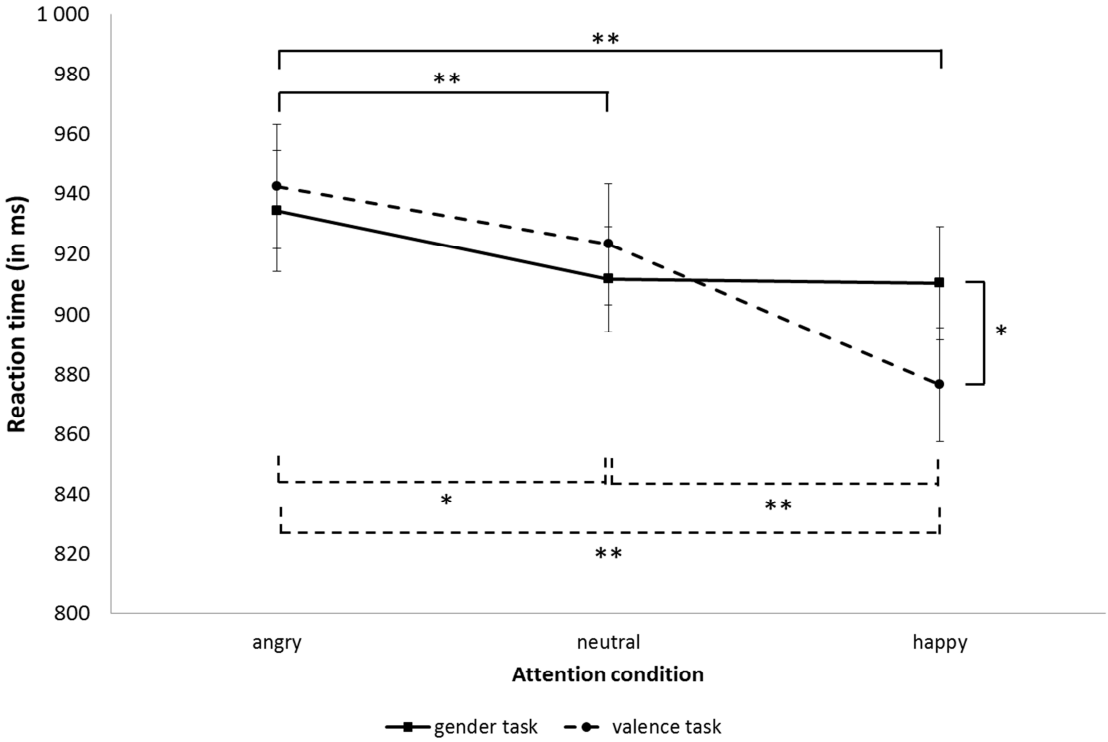

Figure 1. RT data for the Emotion by Attention Condition interaction. Error bars denote standard error of the mean. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). The vertical bar indicates the significant effect for happy faces between both attention conditions. The horizontal bars indicate the significant effect within the valence condition (dotted line) and within the gender condition (full line).

Accuracy

As expected, accuracy rates were higher on the 0-back than on the 2-back task, $F(1, 50) = 128.46$, $p < .001$, partial $\eta^2 = .72$, and accuracy also differed depending on the emotional expression that was shown, $F(2, 100) = 23.35$, $p < .001$, partial $\eta^2 = .32$, with lower accuracies for angry compared to happy ($p < .001$) and neutral faces ($p < .001$). However, this effect of emotion also interacted with Load, $F(2, 100) = 7.65$, $p = .002$, partial $\eta^2 = .13$. In the 0-back task, there was a significant main effect of emotion, $F(2, 100) = 36.49$, $p < .001$, partial $\eta^2 = .42$, with participants being less accurate in response

to angry compared to happy ($p < .001$) and neutral ($p < .001$) faces. In the 2-back task, the main effect of emotion was not significant, $F(2, 100) = 2.96$, $p = .06$, partial $\eta^2 = .06$. Emotion also interacted significantly with Attention condition, $F(2, 100) = 10.34$, $p < .001$, partial $\eta^2 = .17$, with lower accuracies for angry compared to neutral ($p < .001$) and happy faces ($p = .007$), and for neutral compared to happy faces ($p < .001$) in the valence task, and no significant differences in the gender task (see Figure 2).

To follow up these effects, we also calculated accuracy difference scores of [Angry-Neutral] and [Happy - Neutral] for the gender and valence task separately. None of these scores differed significantly between groups (all $p > .21$), and there were no significant correlations with estimated IQ, Total BIS, Total BAS, CDI/BDI z-score or STAI-Trait z-scores for the entire sample or for adolescents and adults separately. An overview of the accuracy and RT data is shown in Table 2.

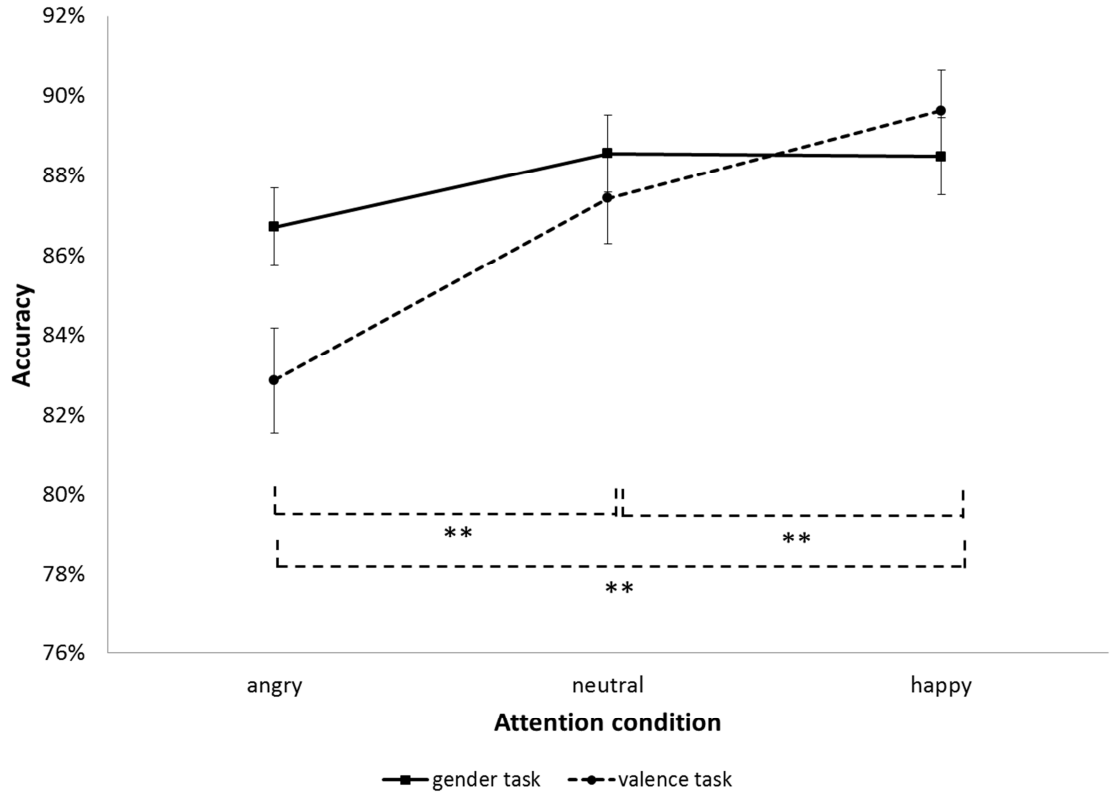

Figure 2. Accuracy data for the Emotion by Attention Condition interaction. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). The horizontal dotted bars indicate the significant effect within the valence condition. Error bars denote standard error of the mean.

Table 2. Reaction times (mean and SD, in ms) and accuracy rates (mean and SD, in %) for adolescents and adults in the 0-back (A) and 2-back task (B)

A. 0-back task

		Adolescents				Adults			
		RT		Acc		RT		Acc	
Attention condition	Emotion	M	SD	M	SD	M	SD	M	SD
Gender task	Angry	879	158	90	8	775	123	93	6
	Happy	870	154	93	8	733	130	98	3
	Neutral	872	149	95	5	749	106	97	4
Valence task	Angry	894	169	88	9	775	139	87	12
	Happy	820	136	95	5	701	128	97	4
	Neutral	885	141	93	8	776	132	96	6

B. 2-back task

		Adolescents				Adults			
		RT		Acc		RT		Acc	
Attention condition	Emotion	M	SD	M	SD	M	SD	M	SD
Gender task	Angry	1042	164	80	10	1076	196	84	10
	Happy	1022	169	79	10	1047	181	84	12
	Neutral	1026	146	79	12	1035	158	83	12
Valence task	Angry	1034	170	77	16	1107	213	79	11
	Happy	977	179	81	14	1024	200	85	10
	Neutral	1019	159	80	13	1046	209	80	14

RT = reaction time
Acc = Accuracy
M = mean
SD = standard deviation

Behavioural correlational analyses

Estimated IQ scores correlated significantly with accuracy in the 0-back task in adolescents (r = .554, p = .005), but not adults (r = -.041, p = .84). No significant correlations were found between performance measures (RT and accuracy on the 0-back, 2-back or entire task, and difference scores for [Angry - Neutral] and [Happy - Neutral] for both attention conditions separately) and questionnaire scores in neither adolescents nor adults.

fMRI data

ROI analysis

Differences in activation for adolescents vs. adults

In the right amygdala, the impact of Load differed for adolescents and adults, as was evident from the significant Load by Group interaction ($F(1, 50) = 4.91$, $p = .031$, partial $\eta^2 = .09$). Even though both adolescents and adults activated the right amygdala more in the 0-back than in the 2-back task ($F(1, 23) = 5.13$, $p = .033$, partial $\eta^2 = .18$ and $F(1, 27) = 23.31$, $p < .001$, partial $\eta^2 = .46$, respectively), this difference ([beta 2-back task – beta 0-back task]) was more pronounced in adults (mean = -.45) than adolescents (mean = -.18) (see Figure 3).

In the left amygdala, there was a significant Group by Emotion by Attention condition interaction ($F(2, 100) = 6.47$, $p = .002$, partial $\eta^2 = .12$), which was likely driven by an Emotion by Attention condition interaction in adolescents ($F(2, 46) = 6.40$, $p = .004$, partial $\eta^2 = .22$) , but not adults ($F(2, 54) = .77$, $p = .47$, partial $\eta^2 = .03$). In adolescents, left amygdala activation differed depending on the emotion that was shown in the gender ($F(2, 46) = 6.78$, $p = .003$, partial $\eta^2 = .23$), but not the valence task ($F(2, 46) = 1.56$, $p = .23$, partial $\eta^2 = .06$). In the gender task, adolescents deactivated the left amygdala less strongly in response to angry compared to happy ($p = .008$) and neutral faces ($p = .01$). Results are shown in Figure 4.

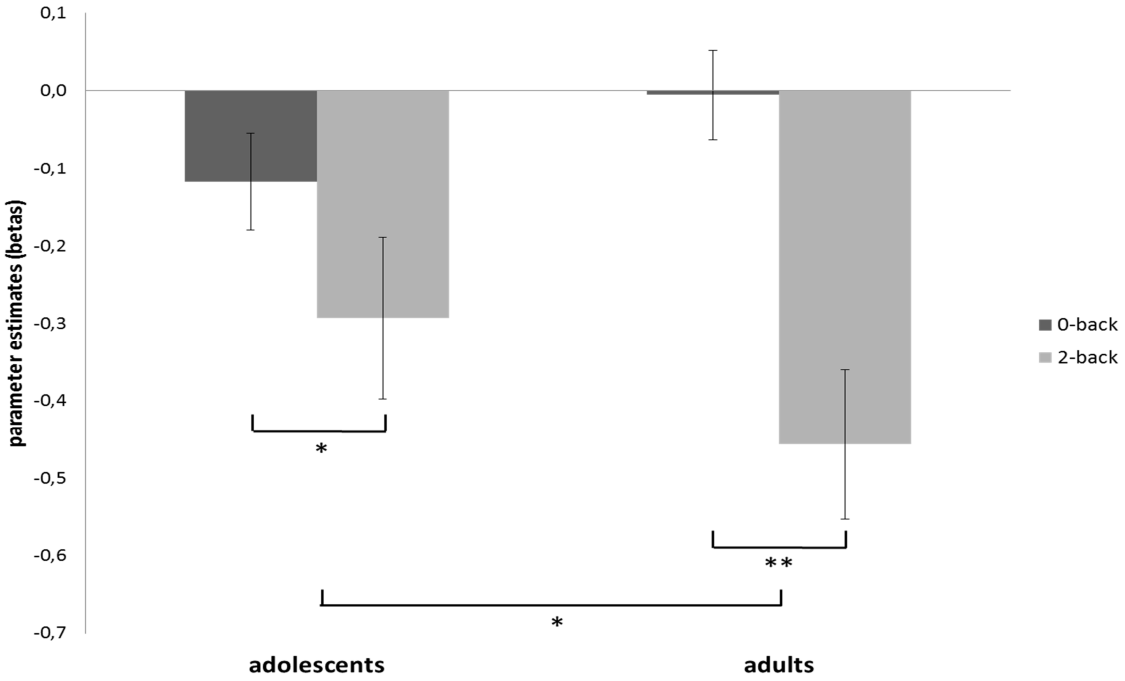

Figure 3. Mean beta estimates in the right amygdala for the 0-back and 2-back task, for adults and adolescents separately. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). Error bars denote standard error of the mean.

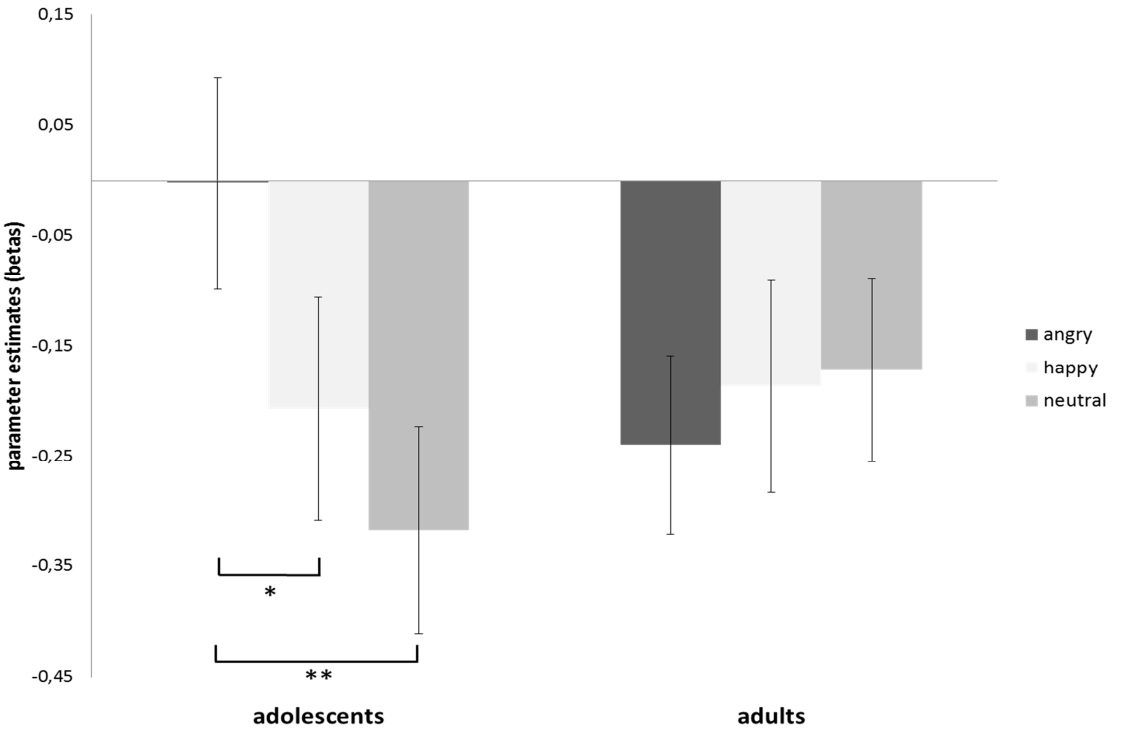

Figure 4.Mean beta estimates in the left amygdala for angry, neutral and happy faces in the gender task for adolescents and adults. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). Error bars denote standard error of the mean.

Two regions showed a significant interaction effect of Group and Emotion, i.e. right DLPFC ($F(2, 100) = 6.02$, $p = .003$, partial $\eta^2 = .11$) and left IFG ($F(2, 100) = 3.47$, $p = .04$, partial $\eta^2 = .07$), as shown in Figure 5. Differential activation for angry, happy and neutral faces was only found in adults (right DLPFC: $F(2, 54) = 6.44$, $p = .003$, partial $\eta^2 = .19$; left IFG: $F(2, 54) = 9.67$, $p < .001$, partial $\eta^2 = .26$), but not adolescents (right DLPFC: $F(2, 46) = 1.43$, $p = .25$, partial $\eta^2 = .06$; left IFG: $F(2, 46) = .19$, $p = .83$, partial $\eta^2 = .008$). In adults, both the right DLPFC and left IFG were activated more strongly in response to angry compared to happy ($p = .005$ and $p = .003$, respectively) or neutral faces ($p = .005$ and $p < .001$, respectively).

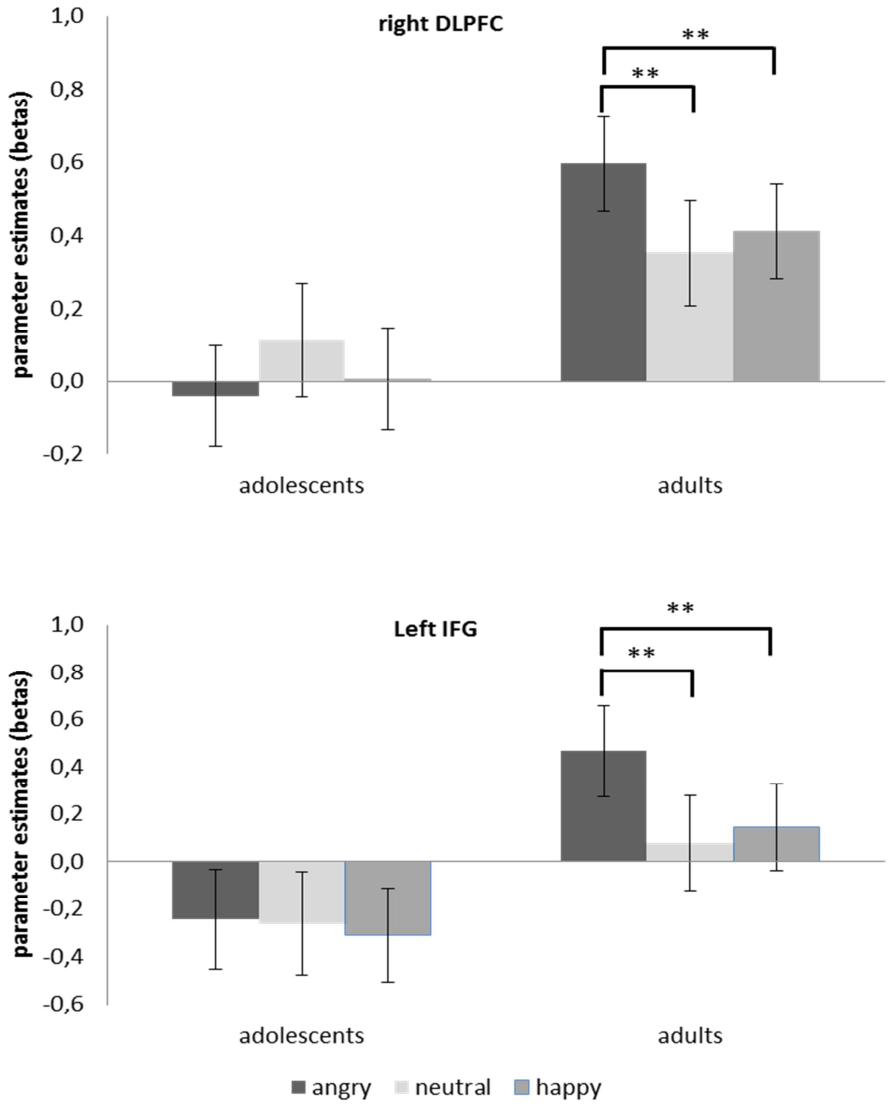

Figure 5. Mean beta estimates for the right DLPFC (upper part) and left IFG (lower part) in response to angry, happy and neutral faces, for adolescents and adults. The asterisk indicates significance at $p < .05$ (*) or $p < .01$ (**). Error bars denote standard error of the mean.

A number of frontal and parietal ROIs, such as the IFJ, MFG, right DLPFC and IPL were found to be increasingly activated in adults compared to adolescents. These regions were also activated more strongly during the 2-back task in comparison to the 0-back task. Decreased activation during 2-back performance was evident in a series of limbic regions, such as the bilateral amygdala and subgenual anterior cingulate cortex (ACC), but also in the occipital cortex, fusiform gyrus and right VS. An overview of regions showing this main effect of Group or Load can be found in Table 3.

Since groups differed significantly on handedness, the ROI analysis (with Load, Emotion and Attention condition as within-subjects and Group as between-subjects factors) was repeated with scores on the Edinburgh Handedness Inventory as covariate of no interest. The main effect of Group in the right fusiform gyrus and right precuneus was no longer significant, but still trending ($F(1, 49) = 3.33$, $p = .074.$, partial $\eta^2 = .06$, and $F(1, 49) = 3.08$, $p = .085.$, partial $\eta^2 = .06$, respectively). Furthermore, the interaction between Emotion and Group in the left IFG just failed to reach significance ($F(2, 98) = 2.84$, $p = .06$, partial $\eta^2 = .06$). All other Group differences reported above remained significant when covarying for handedness.

Effects of Load, Attention condition or emotion, independent of Group

A main effect of Emotion was found in the left occipital gyrus ($F(2, 100) = 7.74$, $p = .001$, partial $\eta^2 = .13$) and right IFJ ($F(2, 100) = 8.41$, $p < .001$, partial $\eta^2 = .11$). The left occipital gyrus exhibited a deactivation in all emotional conditions, but this deactivation was smaller when happy faces were shown compared to neutral faces ($p < .001$). In the right IFJ angry faces resulted in increased activation compared to both happy ($p < .001$) and neutral faces ($p = .007$).

In the right amygdala, Load interacted significantly with Emotion ($F(2, 100) = 6.58$, $p = .002$, partial $\eta^2 = .12$). Follow up tests indicated a main effect of Emotion in the 0-back ($F(2, 100) = 6.76$, $p = .002$, partial $\eta^2 = .12$) but not the 2-back task ($F(2, 100) = .58$, $p = .56$, partial $\eta^2 = .003$). In the 0-back task, activation in the right amygdala was higher for happy and angry compared to neutral faces ($p = .002$ and $p = .02$, respectively).

Exploratory whole brain analysis

Activation in the medial frontal gyrus was increased in adults compared to adolescents. No other regions showed a main or interaction effect with Age group. An overview of regions showing an effect of Load, Attention condition and Emotion can be found in Table 4.

Neural correlates of performance and questionnaire measures

In adolescents, RT on the 0-back task was positively correlated to activity in the left amygdala (r = .64, p = .001), left subgenual ACC (r = .51, p = .011), right subgenual ACC (r = .55, p = .006), left VS (r = .57, p = .004), right VS (r = .55, p = .006) and right medial globus pallidus (r = .51, p = .01). Other performance measures were not significantly correlated with activity in any of the ROIs. In adults, accuracy across the whole task was significantly positively correlated with activation in the left IPL (r = .54, p = .001), left IFG (r = .52, p = .004), left insula (r = .49, p = .009), MFG (r = .51, p = .006), right DLPFC (r = .61, p = .001), right fusiform gyrus (r = .57, p = .001), right IFJ (r = .49, p = .008) and right medial frontal gyrus (r = .58, p = .001). No significant correlations were found between beta weights and questionnaire measures, neither in adolescents nor adults.

Relation between group differences in activation and performance measures

Since the ROI analysis indicated group differences in right amygdala activation on the 2-back compared to the 0-back task, beta weights for these conditions were correlated with performance measures. However, none of these correlations were significant in adolescents (all p > .28) nor adults (all p > .38).

Similarly, since adolescents deactivated the left amygdala less strongly for angry compared to happy and neutral faces in the gender task, we correlated the beta weights of the left amygdala in this condition with the corresponding RT and accuracy. However, no significant correlations were found between beta weights for angry, happy or neutral faces in the gender task and RT or accuracy in the same condition, in adolescents (all p > .33) nor adults (all p > .52).

Table 3. Main effects of Age group and Load in the regions of interest

		ROI peak coordinates			adults > adolescents	2-back > 0-back	0-back > 2-back
hemisphere	region	x	y	z	p-value	p-value	p-value
R	inferior frontal junction	45	9	27	< .001	ns	ns
L/R	superior/medial frontal gyrus	2	17	47	.001	.014	ns
R	dorsolateral prefrontal cortex	36	47	22	.042	< .001	ns
L	inferior frontal junction	-42	4	29	ns	< .001	ns
L	occipital cortex (V1/V2)	-20	-96	5	ns	ns	.044
R	medial globus pallidus	10	-1	-7	ns	ns	ns
R	putamen	23	19	-2	ns	.043	ns
L	inferior parietal lobule	-34	-54	51	.04	< .001	ns
R	medial frontal gyrus	17	1	58	ns	ns	ns
L	subgenual anterior cingulate cortex	-8	17	-17	ns	ns	< .001
R	fusiform gyrus	44	-55	-13	.017	ns	< .001
L	insula	-31	18	-8	.011	ns	ns
R	fusiform gyrus	44	-70	-10	.029	ns	< .001
R	precuneus	30	-74	31	.038	ns	ns
R	dorsolateral prefrontal cortex	42	32	23	.026	< .001	ns
R	subgenual anterior cingulate cortex	7	15	-20	ns	ns	< .001
L	inferior frontal gyrus	-51	31	16	ns	ns	ns
R	amygdala				ns	ns	< .001
L	amygdala				ns	ns	< .001
R	ventral striatum	9	9	-8	ns	ns	.025
L	ventral striatum	-9	9	-8	ns	ns	ns

Note: no regions exhibited significantly greater activity in adolescents compared to adults
Coordinates are reported in MNI space
ns = not significant

Table 4. Results of the whole brain analysis

		Peak coordinate				
region	# voxels	x	y	z	BA	t-score
adults > adolescents						
medial frontal gyrus	45	0	8	52	6	4,18
2-back > 0-back						
right (para)hippocampus	22	30	-22	-11	28	-3,98
left (para)hippocampus	40	-30	-22	-11	28	-5,38
left medial frontal gyrus	638	-3	53	28	9	-6,01
left posterior cingulate gyrus	140	-3	-43	28	23	-5,6
left inferior parietal lobule	32	-45	-40	46	40	-4,52
right inferior parietal lobule	61	39	-43	46	40	-5,26
right mid frontal gyrus	77	24	2	49	6	-4,65
left mid frontal gyrus	159	-21	-4	55	6	-5,68
0-back > 2-back						
right fusiform gyrus	26	42	-49	-17	37	5,69
left lingual gyrus	3501	-15	-70	-5	18	8,16
right superior temporal gyrus	151	63	-1	-5	22	5,08
left superior temporal gyrus	392	-54	-37	10	22	5,7
left insula	36	-45	-1	10	13	5,36
right postcentral gyrus	35	57	-13	25	2	4,31
gender task > valence task						
right inferior temporal gyrus	36	51	-73	4		4,37
left mid frontal gyrus	30	-24	-1	46	6	4,21
Angry > Neutral & Happy > Neutral						
right mid temporal gyrus	21	63	-31	1	22	12,53
Angry > Neutral & Happy > Neutral in the 0-back task						
left superior temporal gyrus	37	-57	-28	1		10,59
Angry > Happy & Happy > Neutral in the 2-back valence task						
left cingulate gyrus	33	-12	32	25	32	12,17

Given group differences in right DLPFC and left IFG activation when angry, neutral and happy faces were presented, we correlated beta weights with performance measures for each emotion condition separately. In adolescents, beta weights in left IFG were positively correlated with RTs for angry faces ($r = .50$, $p = .03$), whereas correlations for neutral ($r = .40$, $p = .10$) and happy faces ($r = .38$, $p = .13$) were not significant. Correlations between left IFG activity and accuracy was not significant for any of the emotion conditions (all $p > .44$). In adults, a significant correlation was found between left IFG activation and both RT ($r = -.42$, $p = .03$) and accuracy ($r = .48$, $p = .02$) when neutral faces were presented. For happy faces, activity in this region was positively correlated with accuracy ($r = .52$, $p = .01$) but not with RT ($r = -.24$, $p = .22$), and for angry faces there was no correlation with either RT ($r = -.35$, $p = .14$) or accuracy ($r = .34$, $p = .16$). In right DLPFC, adolescents did not show significant correlations between parameter estimates and performance measures in each emotion condition (all $p > .84$). But in adults, right DLPFC activity correlated with accuracy in the happy ($r = .60$, $p = .002$) and neutral condition ($r = .57$, $p = .002$), while this effect was only trending for angry faces ($r = .37$, $p = .07$). Furthermore, RTs also correlated significantly with right DLPFC activation for neutral faces ($r = -.42$, $p = .027$), but not for happy faces ($r = -.23$, $p = .24$). The correlation with RTs for angry faces was trending ($r = -.40$, $p = .07$).

DISCUSSION

The present study used an emotional n-back task to assess developmental differences in neurobiological functioning underlying working memory processing of emotional information. Based on neurobiological theories (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), we hypothesized to find increased activation in subcortical limbic areas, such as the amygdala and ventral striatum, combined with a hypo-activation of prefrontal regions responsible for cognitive control, such as the dorsolateral prefrontal cortex, inferior frontal gyrus and medial frontal gyrus, in adolescents compared to adults. Results generally supported our hypotheses, with adolescents showing increased activation in bilateral amygdala and decreased

activation in several prefrontal regions, especially right dorsolateral prefrontal cortex and left inferior frontal gyrus. However, no differences between age groups were found in the ventral striatum.

At the behavioural level, there were no group differences, in contrast to the results of the study reported in Chapter 3. Although the same task was used in both studies, some changes were necessary to adapt it to the fMRI environment. The inter-trial interval was jittered, affecting the response-cue interval, and blocks had a fixed duration. These factors could have influenced performance on the experimental task. Furthermore, the fMRI environment might have made it more difficult for participants, especially adolescents, to focus on the task due to scanner noise, and participants were probably more anxious compared to when the task was performed in a quiet laboratory environment. Another difference concerns the age range of the adolescent sample, which was broader in the current study, i.e. between 12 and 16 years of age, compared to between 12 and 14 years of age in Chapter 3. Therefore, the findings reported in the previous chapter might be restricted to a younger adolescent sample. Finally, given that the behavioural group difference in Chapter 3 had a relatively small effect size (partial $\eta^2 = .05$), the current study could have lacked power to detect this effect given the smaller sample size ($n_{adolescents} = 24$ and $n_{adults} = 28$ in the current study, compared to $n_{adolescents} = 37$ and $n_{adults} = 33$ in Chapter 3). In general, fMRI studies comparing groups, especially developmental populations, often fail to find behavioural effects (Britton, Gold, Deckersbach, & Rauch, 2009; Leibenluft et al., 2007; Mincic, 2010; Nelson et al., 2007). And whether or not there are behavioural differences on the emotional n-back task between adolescents and adults, the main goal of the current study is to examine group differences in brain activation.

On a neurobiological level, developmental differences emerged both in prefrontal as well as subcortical areas. Relative to adults, adolescents under-recruited a network of fronto-parietal areas that have been found to play a role in cognitive control and attention. Furthermore, in adults, activity in two of these regions (right DLPFC and left IFG) was modulated by the emotional expression of the face that was presented, while adolescents' activity in these regions was irresponsive to an emotional manipulation. More specifically, adults additionally recruited right DLPFC and left IFG

when angry faces were shown compared to when a happy or neutral face was presented. Developmental differences were also found in the bilateral amygdala. In the right amygdala, the increase in activation during the 0-back compared to the 2-back task was more pronounced in adults than adolescents. In the left amygdala, when participants were asked to attend to the gender of a face and thus neglect the emotional expression, adolescents exhibited less deactivation when confronted with an angry as opposed to a happy or neutral face, while adults' left amygdala activity was not sensitive to such manipulations.

The finding that adolescents under-activated a range of fronto-parietal regions compared to adults confirms the results of previous studies investigating the development of cognitive control during adolescence. Structural imaging studies have typically found a delayed maturation of prefrontal areas until about 25 years of age (Giedd, 2004; Giedd et al., 1999; Gogtay et al., 2004), and functional studies have identified developmental patterns of brain activation shifting from a diffuse to focal activation (Bunge & Wright, 2007; Crone, 2009; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Klingberg, Forssberg, & Westerberg, 2002). This pattern is characterized by increased activation with age in areas that are critical to cognitive control performance, and decreased activation in areas that are not critical for task performance. Indeed, in the present study we found stronger activity in adults in areas that have been shown to be involved in cognitive control tasks, such as the right DLPFC, medial frontal gyrus and left IPL (Fassbender et al., 2006; Goldman-Rakic, 1995; Owen, McMillan, Laird, & Bullmore, 2005; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Shomstein, 2012; Wager & Smith, 2003). Importantly, these regions were also increasingly activated during the 2-back task compared to the 0-back task, confirming their role in working memory processing. Additionally, the finding that activity in these regions was related to accuracy scores during the emotional n-back task in adults but not adolescents further supports the idea that functional specialization of this fronto-parietal networks is still under development during adolescence (Bunge & Wright, 2007; Paus, 2005; Satterthwaite et al., 2013).

Interestingly, the modulation of right DLPFC and left IFG by emotional manipulations used in the experimental task differed between groups. More specifically, angry faces were found to activate both regions more strongly than happy

or neutral faces in adults, but not adolescents. Right DLPFC, an area that is crucial for working memory (Barbey, Koenigs, & Grafman, 2013; Curtis & D'Esposito, 2003; Owen et al., 2005; Wager & Smith, 2003), has been linked to the maintenance of task goals (Barbey et al., 2013; Curtis & D'Esposito, 2003; Miller, 2000) and the implementation of top-down attentional control in the face of distraction or interference (Banich et al., 2009; Blasi et al., 2007; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008). Increased activation in right DLPFC in adults could reflect attentional biasing towards relevant and away from irrelevant features of stimuli, i.e. attentional orienting towards emotional information in the valence task and away from the emotional expression in the gender task. The absence of such emotional modulation in right DLPFC in adolescents might indicate that these top-down control mechanisms are not yet in place in this age group, which is in line with the finding that grey matter matures last in the DLPFC, at the end of adolescence (Gogtay et al., 2004). Consistent with this interpretation, activity in the right DLPFC was significantly positively correlated with accuracy in adults, but not adolescents.

Another region showing a differential activation pattern for angry, happy and neutral faces in adults but not adolescents is the left IFG (BA45), a region that has previously been identified as a relay station between ventral and dorsal attentional systems (Anticevic, Repovs, & Barch, 2010; Dolcos & McCarthy, 2006; Mincic, 2010). These studies suggest that the left IFG plays a role in inhibiting the impact of emotional distractors on working memory processes. Our findings indicate that the role of the left IFG in this process is age-dependent. This is also reflected in the absence of a correlation between left IFG activation and accuracy scores in adolescents, while adults showed a negative correlation between both when happy or neutral faces were presented.

Aside from differences in fronto-parietal areas related to cognitive control processes, adolescents and adults also differentially activated subcortical areas, i.e. bilateral amygdala. Left amygdala activation was higher during the gender task when angry faces were shown (compared to happy and neutral faces), but only in adolescents. In the gender task, the emotional expression of the face is irrelevant to the task goal and can thus be considered an emotional distractor. Previous studies

investigating the impact of emotional distractors on working memory performance have also identified increased amygdala activation associated with negative stimuli (Anticevic et al., 2010; Dolcos et al., 2008; Dolcos & McCarthy, 2006), which has been interpreted to reflect greater distractibility. Interestingly, in the current study this effect was only found in adolescents, which might be due to 1) adolescents' hypersensitivity to emotional stimuli as proposed by neurobiological theories, 2) better top-down control mechanisms in adults. The latter interpretation is supported by the finding that left IFG and right DLPFC acitivity was higher for angry compared to happy and neutral faces in adults but not adolescents.

Although both groups showed stronger right amygdala activation for the 0-back compared to the 2-back task, the difference between both was larger in adults. The heightened amygdala activity during the 0-back vs. 2-back task is in line with previous studies indicating decreased amygdala activation to emotional faces under high load (Pessoa, Kastner, & Ungerleider, 2002; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Silvert et al., 2007). These studies have shown that the processing of emotional stimuli is under the influence of top-down control. Our results suggest that increasing the cognitive load can dampen amygdala activity in response to emotional stimuli both in adults and adolescents, although the decrease in amygdala activation was smaller in the latter group. Neurobiological theories of adolescent behaviour might attribute this to their immature cognitive control system or hypersensitivity to emotional stimuli (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008). However, the latter explanation is unlikely given that right amygdala activation was not significantly different in both groups in the 0-back and 2-back task. Indeed, only the difference in activation between both tasks was significantly larger in adults than adolescents. The immaturity of the cognitive control network, on the other hand, might offer an explanation for these findings. Due to this immaturity, adolescents might be less able to regulate activation in the amygdala when load increases.

The amygdala hyper-activation in adolescents that was seen in this study extends similar findings from previous studies (Guyer, Monk, et al., 2008; Hare et al., 2008; Monk et al., 2003) and confirms hypotheses derived from neurobiological theories of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008). However, based on these theories, we would also expect to find developmental

differences in reward-related brain areas, such as the ventral striatum (VS). Even though previous research has consistently shown heightened recruitment of the VS, and more specifically the nucleus accumbens, in adolescents in the context of reward (Ernst et al., 2005; Galvan et al., 2006; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011), findings are mixed when other affective stimuli, such as happy faces, are used (Hare et al., 2008; Somerville, Hare, & Casey, 2011). Given that the evidence in this regard is rather scarce, future research is needed to elucidate the exact role of the ventral striatum.

Limitations

There are some limitations in the current study that should be addressed. First, groups differed on handedness. While there were only 2 ambi-dextrous and no left-handed participants in the adult group, the adolescent group included 6 ambi-dextrous and 3 left-handed participants. However, given that all group differences either remained significant or showed a very strong trend when covarying for handedness, this factor did not seem to have a large impact on our findings. Second, for group differences in the ROI analysis, we did not correct for the amount of regions. Instead, we used a lenient threshold of $p < .05$ for each ROI, given the exploratory nature of this study. Third, given that a control group of pre-adolescent children was not included in the current study, it is unclear whether the effects reported here are specific to adolescents. Future studies should therefore include younger age cohorts to examine the developmental trajectory of the functioning of prefrontal and subcortical areas in studies examining emotion-cognition interactions.

Conclusion

In summary, the present study extends previous findings of diminished prefrontal functioning in adolescents relative to adults. Importantly, activity in two of our regions of interest within the prefrontal cortex (right DLPFC and left IFG) depended on the emotional expression that was shown in adults, but not adolescents. Developmental differences were also evident in subcortical regions, i.e. bilateral amygdala, with increased activation in adolescents compared to adults. These findings

are in line with neurobiological theories of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), although no developmental differences were found in the ventral striatum. Future studies are needed to examine whether our findings are specific to adolescents and how these differences in prefrontal and amygdala functioning are related to adolescent behaviour patterns, such as risk-taking and emotional instability.

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CHAPTER 5

CHILDHOOD ABUSE IMPACTS WORKING MEMORY FOR POSITIVE EMOTION IN FEMALE UNIVERSITY STUDENTS[1]

ABSTRACT

Childhood abuse is an important risk factor for depression, anxiety disorders, and substance use later in life. One possible mechanism underlying this association could be deficits in cognitive processing of emotional information. This study tested the impact of distracting emotional information on working memory performance in 21 young women with a history of sexual and physical abuse during childhood/adolescence (mean age = 20.0), and compared their performance to 17 individuals reporting nonabuse-related childhood stress (mean age = 19.6) and a control group of 17 women without a history of childhood stress (mean age = 20.0). During the most difficult distractor condition, working memory accuracy for positive versus neutral incidental emotional stimuli was reduced in women reporting a history of abuse relative to both control groups (with and without nonabuse-related childhood stress). The current results reveal aberrant responses to positive stimuli and are consistent with the notion of persistent influence of childhood abuse on processes critical for emotional well-being and emotion control.

[1] Based on Cromheeke, S., Herpoel, L. & Mueller, S.C. (2014). Childhood abuse impacts working memory for positive emotion in female university students, *Child Maltreatment, 19*(1), 38-48. doi: 10.1177/1077559513511522

INTRODUCTION

Traumatic events and experience of early stress (ES) during childhood or adolescence, such as parental loss, witnessing violence or sexual or physical abuse have been linked to a variety of adverse health outcomes during the lifespan (McCrory, De Brito, & Viding, 2010). More specifically, these experiences have been shown to be an important risk factor for development of later psychopathology, such as depression, post-traumatic stress disorder, anxiety, and substance abuse (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001). Importantly, childhood sexual abuse is particularly related to psychopathology even when other adversities and stressors are taken into consideration (Molnar, Buka, & Kessler, 2001). In order to develop interventions aimed at diminishing the adverse effects of such traumatic childhood stress later in life, it is crucial to gain insight into the underlying cognitive mechanisms linking early-life stress to psychopathology.

Current research suggests two possible pathways for reduced health and quality of life in victims of childhood maltreatment. These pathways center around 1), reduced cognitive control and self-regulatory abilities and 2), dysfunctional emotion processing. Although limited, on the one hand, previous work in individuals with experience of ES has documented impairments in cognitive control such as inhibition (Carrion, Garrett, Menon, Weems, & Reiss, 2008; De Bellis, Hooper, Spratt, & Woolley, 2009; Jovanovic et al., 2012; Lewis, Dozier, Ackerman, & Sepulveda-Kozakowski, 2007; Mueller et al., 2012), response shifting (Mueller et al., 2010), and working memory (Majer, Nater, Lin, Capuron, & Reeves, 2010). Due to the frequent co-occurrence of multiple stressors (Green et al., 2010), most of these previous studies have included individuals with different types of early-life stress, such as neglect and maltreatment (Mueller et al., 2010), emotional abuse, sexual or physical abuse and/or neglect (Majer et al., 2010) and youth who experienced physical or sexual abuse, or witnessed violence (Carrion et al., 2008). By comparison, only a few of these studies have differentiated between types of stressors and have taken the severity of the early-stress experience into account (De Bellis et al., 2009; Majer et al., 2010). In contrast to the limited work on cognitive impairments in ES, much research has documented detrimental changes in processing emotions after emotional neglect and maltreatment (Maheu et al., 2010;

Masten et al., 2008; Tottenham et al., 2010). For example, individuals with a history of maltreatment show abnormalities in emotional face recognition, especially in negatively-valenced faces and exhibit a hyper-responsivity to both angry (Curtis & Cicchetti, 2011; Fries & Pollak, 2004) and fearful faces (Masten et al., 2008).

Even though both pathways, i.e. reduced cognitive control and impaired emotion processing, are important to understand the relationship between ES and psychopathology, increasing efforts, which focus on the tight and dynamic interplay between emotion and cognitive control (Cromheeke & Mueller, 2013; Pessoa, 2009), suggest that these two pathways might not be independent. Dove-tailing this interplay, a study that investigated the effects of reward on cognitive control reported improvements in inhibitory control with reward in healthy adolescents but not adolescents with a history of maltreatment and emotional neglect, which suggests stress-related deficits in the processing of positive information (Mueller et al., 2012). However, apart from studies examining information processing changes associated with reward (e.g. Guyer et al., 2006; Milner et al., 2011; Mueller et al., 2012), no study to our knowledge has investigated how other positive and negative emotional stimuli influence cognitive control processes in individuals reporting severe trauma such as physical and sexual abuse. However, cognitive research suggests a change in the processing of positive and negative child-related schemata in children at-risk for physical abuse relative to low-risk children (Milner et al., 2011). Recent work demonstrated that the ability to update positive information in working memory was positively linked to life satisfaction and balanced affect (Pe, Koval, & Kuppens, 2013). Such findings might provide important clues to building resilience and establishing effective therapeutic interventions for survivors of abuse and early stress (e.g. Fisher, Chamberlain, & Leve, 2009; Healey & Fisher, 2011; Pe et al., 2013). Since studies investigating emotion-cognition interactions in maltreatment are scarce, evidence in disorders for which individuals with experience of maltreatment have high propensity might provide helpful links.

In a meta-analysis on the emotional Stroop task, depressed individuals, relative to healthy comparisons, exhibited consistent attentional biases for both negative and positive stimuli albeit not as strong in the latter (Epp, Dobson, Dozois, & Frewen, 2012). In-line with this view, remitted depressed individuals show differential neural responses

during fMRI to positive (hypoactivation) and negative (hyperactivation) distracting emotion in the prefrontal cortex during a working memory task (Kerestes et al., 2012). In anxious individuals, less evidence is available but shows for example slowed updating of working memory during positive emotion in high anxious vs. low anxious children (Visu-Petra, Tincas, Cheie, & Benga, 2010). These empirical data support suggestions of a link between cognitive control abilites such as working memory and emotion regulation and emotion control processes (Joormann & D'Avanzato, 2010; Joormann & Gotlib, 2008, 2010; Schmeichel & Demaree, 2010; Schmeichel, Volokhov, & Demaree, 2008), further underlining a tight interplay between affective and executive processes.

The current study sought to address how emotional stimuli interfere with cognitive control processes, such as working memory, in young women with a history of childhood sexual and physical abuse. To assess specificity of adverse childhood experience on emotion processing, a second group of young women who had experienced other childhood adversities were also included in addition to a control group with no history of ES, given that different types of childhood stress have been found to result in distinct outcomes (Bruce, Fisher, Pears, & Levine, 2009; McCrory et al., 2010). Based on 1) findings in individuals with mood and anxiety disorders (Joormann & Gotlib, 2008; Stout, Shackman, & Larson, 2013), 2) a high vulnerability of sexually and physically abused individuals to develop such psychopathology (Chou, 2012; Green et al., 2010) and 3), the severity of childhood sexual/physical abuse relative to other adversities (Molnar et al., 2001), three main predictions were made. First, it was hypothesized that the abuse group would show impaired working memory performance during emotional distractors relative to 1) a neutral condition, 2) individuals reporting a history of non-abuse related childhood stress and 3) healthy comparisons in a visuo-spatial working memory task. Finally, we also predicted that both groups with a history of childhood stress would show higher rates of self-reported psychopathology than the control group.

METHOD

Participants

First-year university psychology students (n = 616) were asked to complete several screening questionnaires in exchange for course credit. For the present purposes, students were asked to indicate the number of stressors they had encountered during childhood and/or adolescence (0, 1, 2 or more). Due to ethical reasons, no questions were asked regarding the specificity of stressors at that moment. To recruit female participants with a history of physical/sexual abuse, we invited individuals who reported two or more early life stressors on the initial screening (n = 78) into the laboratory, of whom 40 voluntarily agreed to participate in the study and fill in additional questionnaires. All participants came from a homogenous background in Flanders and were of Caucasian ethnicity. To assess the nature of the stressors more specifically, upon visiting the laboratory participants completed the Stressful Life Events Screening Questionnaire (SLESQ) (Goodman, Corcoran, Turner, Yuan, & Green, 1998), a 13-item self-report measure to determine exposure to eleven specific and two general categories of events (e.g. life-threatening accident, sexual, physical, or emotional abuse). For each category, participants were asked to indicate whether they had experienced such an event and, if they responded 'yes', to specify the event (e.g. age, frequency, duration). The SLESQ has a good test-retest reliability (median κ = .73) and adequate convergent validity (median κ = .64) (Goodman et al., 1998). In the current sample, the internal consistency of the SLESQ was acceptable (α = .6). To assess sexual and physical abuse specifically, the questionnaire includes the following items: "1) At any time, has anyone (parent, other family member, romantic partner, stranger or someone else) ever physically forced you to have intercourse, or to have oral or anal sex against your wishes, or when you were helpless, such as being asleep or intoxicated?, 2) Other than experiences mentioned in earlier questions, has anyone ever touched private parts of your body, made you touch their body, or tried to make you to have sex against your wishes?, 3) When you were a child, did a parent, caregiver or other person ever slap you repeatedly, beat you, or otherwise attack or harm you?". For the abuse group, only female students who had reported either sexual abuse (n = 10), physical abuse (n = 4), or a combination of both (n = 7) were selected (Total N = 21,

mean age (M_{age} = 20.0 years, standard deviation (SD) = 1.9). Students reporting other experiences of childhood stress, such as illness or accidents, were included in the non-abuse stress group (n = 17, M_{age} = 19.6 years, SD = 1.1). The control group consisted of 17 female students (n = 17, M_{age} = 20.2 years, SD = 1.7) who did not report any prior or current stressful life events in the SLESQ (details of experienced stressors in Table 1). All participants agreed to voluntarily take part in the experiment in exchange for course credits or monetary compensation. The study was approved by the ethical committee of the Faculty of Psychology and Educational Sciences at Ghent University.

To assess the presence of psychopathology, participants completed the Dutch version of the Adult Self Report (ASR; Achenbach & Rescorla, 2003), a screening instrument measuring mental health problems (internalizing and externalizing), resulting in scores on both syndrome scales and DSM (Diagnostic and Statistical Manual of Mental Disorders) scales. The ASR has a good reliability and content validity, and excellent internal consistency (α = .94 (Evers, van Vliet-Mulder, & Groot, 2005); α = .95 in the current sample). T-scores higher than 63 on the subscales Internalizing problems, Externalizing problems and Total problems are considered clinical. Current levels of depression and anxiety were assessed with the Beck Depression Inventory (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961) and State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) (Table 2). Both the BDI-II-NL and STAI-NL have good validity and excellent internal consistency (α = 0.88 and α = 0.9 respectively (Evers et al., 2005); in the current sample: α = 0.93 for BDI, α = 0.92 for STAI-State, α = .94 for STAI Trait). Since resilience has been shown to moderate the presence and severity of depression following childhood trauma (Wingo et al., 2010), we also included the Resilience Scale (RS-NL; Wagnild & Young, 1993), a 25-item questionnaire with good internal consistency (α = 0.85; in the current sample: α = 0.80), test-retest reliability (r = 0.9) and acceptable construct validity (Portzky, Wagnild, De Bacquer, & Audenaert, 2010).

Stimuli and material

Images of 44 different actors (24 male, 20 female) were selected from the NimStim face stimulus database (Tottenham et al., 2009) and the Radboud Faces Database (Langner et al., 2010). Each actor posed three emotional expressions (neutral,

happy, angry) with closed mouth, resulting in a total of 132 faces. Only pictures with emotion ratings of 70% or higher (mean emotion rating: 94%) for all three emotions were selected (Langner et al., 2010; Tottenham et al., 2009). To avoid confounds based on external features, background and hair were removed, and images were gray-scaled (256 gray levels) using Adobe Photoshop 5.0. The faces were displayed on a black background at 160x200 pixels, corresponding to approximately 4x5cm. At the beginning of the experiment 30 individuals (15 male, 15 female) were randomly chosen from the selection of 44 actors. Each actor only expressed one emotion throughout the task, resulting in 10 individuals per emotion (five male, five female). The task consisted of 120 trials divided into four blocks of 30 trials each. Within each block, every actor was shown once. After completing the task, participants were asked to fill in the questionnaires.

Procedure

The sequence of the Spatial Emotional Match To Sample (SEMTOS) task, modeled after a non-emotional variant of Awh et al. (Awh, Jonides, & Reuter-Lorenz, 1998), during a single trial was as follows (Figure 1): a) A yellow fixation cross was shown at the beginning of the trial for 1 sec, b) the memory cue (a happy, angry or neutral face) appeared for 400 ms in one of 24 possible locations. The locations were equally spaced on an imaginary concentric circle with a radius of 250 pixels. To prevent verbal coding of locations, every possible location was located at least 10° clockwise or counterclockwise from the cardinal axes, c) during a retention interval of 5000 ms, a red or blue color probe was shown for 1000 ms. Participants were asked to indicate the color of this stimulus by pressing the red or blue button (‘w’ or ‘x’ on the keyboard, covered with red and blue stickers, respectively) with the left hand. The interval between the end of the memory cue and the appearance of the color probe varied randomly between 1000 ms and 3000 ms, d) after the retention interval, the face was shown again for 1500 ms. Participants had to indicate whether this memory probe had the same location as the memory cue that was shown at the beginning of the trial. They were instructed to press “=” for match trials and “≠” for miss trials (“:” and “=” on the keyboard, covered with stickers of “=” and “≠”, respectively), using their right hand.

Before starting the experiment, both the memory and the color discrimination tasks were practiced separately first, and then together. Each practice block consisted of 10 trials. Participants only continued to the next block if they had an accuracy rate of at least 60%. They were asked to look at the fixation cross at the beginning of each trial, when the fixation cross turned yellow. For both the memory probe and color probe, only responses within a response window of 2000 ms were registered. Participants were instructed to respond as quickly as possible, but without compromising accuracy. They did not receive feedback about their performance on either task.

The location of the memory probes matched the memorized location on 40% of the trials (match trials). When the locations did not match (miss trials), the distance between the memory cue and probe was varied systematically between 15° (Miss1), 20° (Miss2) and 25° (Miss3) clockwise or counterclockwise on the imaginary concentric circle, respectively. The emotional expression and gender of the faces was counterbalanced across these conditions. The distance between the memory cue and the color probe varied systematically. Color probes were shown either near (40° on the imaginary circle) or far (160° on the imaginary circle), and either clockwise or counterclockwise from the memorized location.

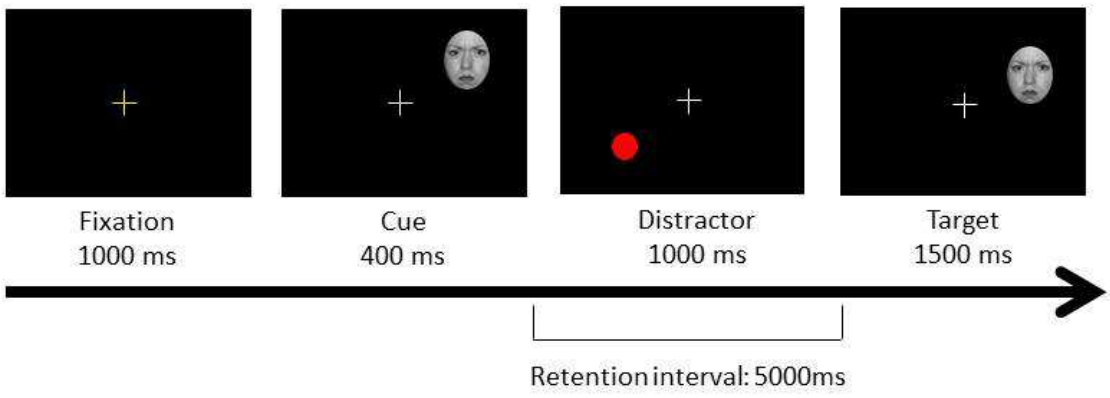

Figure 1. Overview of a typical trial in the SEMTOS task.

Statistical analysis

A 4 x 3 x 3 repeated measures analysis of covariance (ANCOVA) on responses to the memory probe was conducted with Location (Match, Miss1, Miss2, Miss3) and Emotional expression (angry, happy, neutral) as within-subjects factors and Group (abuse, stress, and control group) as between-subjects factor. The ANCOVA was run twice, once for accuracy (% correct) and once for reaction times (in ms). Significant interactions or main effects were followed-up with pairwise comparisons, paired samples t-tests, or univariate analyses, as appropriate. Mean reaction times were based on correct trials. Reaction times of less than 100 ms were excluded as anticipatory responses. Additional correlational analyses (Pearson's r) were carried out to investigate the association of the behavioural findings with results of mood state and psychopathology as well as individual factors of abuse (e.g., age of onset, duration, frequency of abuse). Measures of effect size are reported as Cohen's d or partial eta squared (as appropriate).

RESULTS

Table 1.
Detailed information on reported stressors as assessed with the Stressful Life Events Screening Questionnaire (SLESQ) for the control, stress, and abuse group, separately.

SLESQ item	Controls (n = 17)	Stress group (n = 17)	Abuse group (n = 21)
Life-threatening illness/accident	0	3	7
Robbery/mugging	0	1	2
Death of a close friend/relative	0	5	6
Sexual abuse with physical force	0	0	12
Sexual abuse without physical force	0	0	7
Childhood physical abuse	0	0	11
Adulthood physical abuse	0	2	4
Emotional abuse	0	6	12
Threatened with a weapon	0	0	1
Witnessed violence or physical/sexual abuse	0	2	8
Other experiences of serious injury or life in danger	0	0	2
Other frightening experiences[a]	0	7	8

[a]Examples include a car accident, witnessing an explosion, suicide attempt of a parent, life-threatening illness of a parent

Table 2.
Demographic information and mean scores (SD) on the measures of anxiety (STAI), depression (BDI), psychopathology (ASR), mean number of stressors, and resilience score.

Variable	Control group (n = 17)	Stress group (n = 17)	Abuse group (n = 21)	p-value	Effect size partial η^2
Age	20.21 (1.73)	19.56 (1.13)	20.04 (1.93)	.50	.03
Depression [a]	-.51 (.54)	.32 (1.08)	1.04 (1.49)	.001	.25
State anxiety [a]	-.42 (.87)	.43 (1.03)	.38 (1.26)	.04	.12
Trait anxiety[a]	-.49 (.75)	.63 (1.28)	.77 (1.21)	.002	.21
Total Psychopathology[b]	45.35 (4.12)	56.62 (9.08)	59.2 (11.81)	< .001	.32
Number of stressors	0 (0)	1.41 (0.94)	3.81 (1.25)	< .001	.76
Resilience[b]	49.35 (6.69)	47.88 (7.87)	45.86 (8.65)	.39	.04

[a]z-scores are shown for BDI, STAI-trait and STAI-state.
[b]T-scores are used

Questionnaire results

Table 1 shows details of the type and number of stressors reported by the control, stress and abuse group. Groups differed significantly on the mean number of stressors with the abuse group reporting more stressors than the stress group, and both the abuse and stress group reporting more stressors than the control group ($p < .001$ for all pairwise comparisons, Bonferroni corrected). Table 2 shows the demographic and psychopathology indicators by the control, stress and abuse group. Age or resilience scores did not differ between groups. However, significant group differences were found on trait levels of anxiety, state levels of anxiety, and symptoms of depression. Post-hoc tests indicated that both the stress and abuse group scored higher than controls on trait ($p = .005$ and $p = .001$, respectively) and state anxiety ($p = .026$ and $p = .028$, respectively). The abuse group also reported more symptoms of depression than controls ($p < .001$), while the difference between the stress and control group on this measure approached conventional levels of significance ($p = .059$). In terms of psychopathology, while none of the participants in the control group met clinical cut-off scores, eight out of 17 women in the stress group and eight out of 21 women in the abuse group scored within the clinical range on internalizing and externalizing scales, a difference that was significant, χ^2 (2, N = 54) = 111.06, $p = .004$. Participants also differed on the total psychopathology (ASR) scores, with women in the abuse and stress

group scoring significantly higher than control women ($p < .001$ and $p = .003$, respectively). Given the group differences in levels of depression and anxiety, these variables were added as covariates in the subsequent analyses (but we do not discuss them as they were not the focus of our hypotheses).

Accuracy

As expected, the three-way Location by Emotion by Group interaction was significant, $F(12, 300) = 2.02$, $p = .023$, partial $\eta^2 = .08$. To follow-up this interaction, the analyses were re-run split at the level of Group (Figure 2, Table 3). Location significantly interacted with Emotion in the abuse, $F(6, 108) = 2.32$, $p = .04$, partial $\eta^2 = .11$, and the stress group, $F(6, 84) = 2.42$, $p = .03$, partial $\eta^2 = .15$. In the control group, however, this interaction was not significant.

The Emotion by Location interaction in the abuse group showed that in the most difficult distractor condition, the Miss1 trials, women with a history of abuse performed significantly worse for happy compared to neutral faces ($p = .022$) (see Figure 2A). By comparison, an impact of affective valence was not present in Match trials or in easier to detect Miss2 or Miss3 trials. In the stress group, follow-up analyses for each location separately did not yield any significant main effects of emotion, although there was a slight trend in the Miss3 trials, $F(2, 32) = 2.61$, $p = .09$, partial $\eta^2 = .14$). In addition, the main ANCOVA analysis also revealed a significant main effect of Location, $F(3, 150)= 74.58$, $p < .001$, partial $\eta^2 = .60$, which indicated a higher accuracy for match trials and trials farthest from the target (Miss3) than for distractors closer to the target (Miss1 and Miss2 trials) (all pairwise comparisons $p < .001$, Bonferroni corrected) regardless of Group.

To further assess the difference in responding to Miss1 happy faces in the abuse group, difference scores of emotional valence [Neutral – Happy] and [Neutral - Angry] were calculated (Figure 3). Confirming the findings from the main analysis, the [Neutral – Happy] accuracy difference score was significantly different from 0 in the abuse group, $t(20) = 2.48$, $p = .022$, $d = 0.56$, but not in the stress group or the control group. By comparison, the [Neutral - Angry] accuracy difference score in the Miss1 trials did not differ significantly from 0 in the abuse, stress or control group.

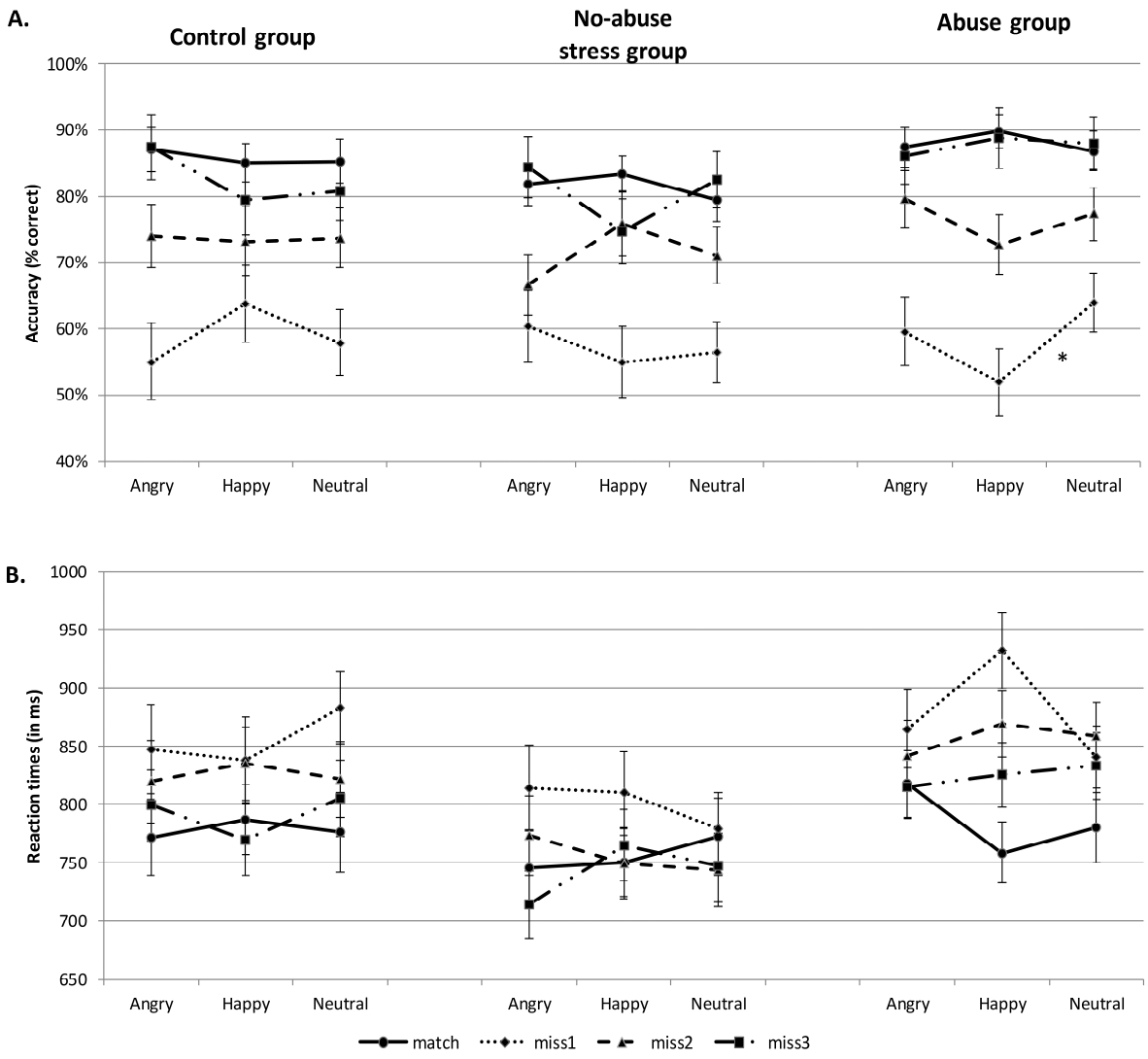

Figure 2. A. Accuracy scores (% correct) for the control (left panel), no-abuse stress group (middle panel), and abuse group (right panel) split by emotional valence and location. **B.** Reaction times (ms) for the control (left panel), no-stress abuse group (middle panel), and abuse group (right panel), split by emotional valence and location of the stimuli. Full lines indicate match trials, dotted lines are Miss1 trials, dashed lines are Miss2 trials and the combined dashed/dotted lines are Miss3 trials. Error bars denote SEM. Asterisk indicates significance, $p < .05$

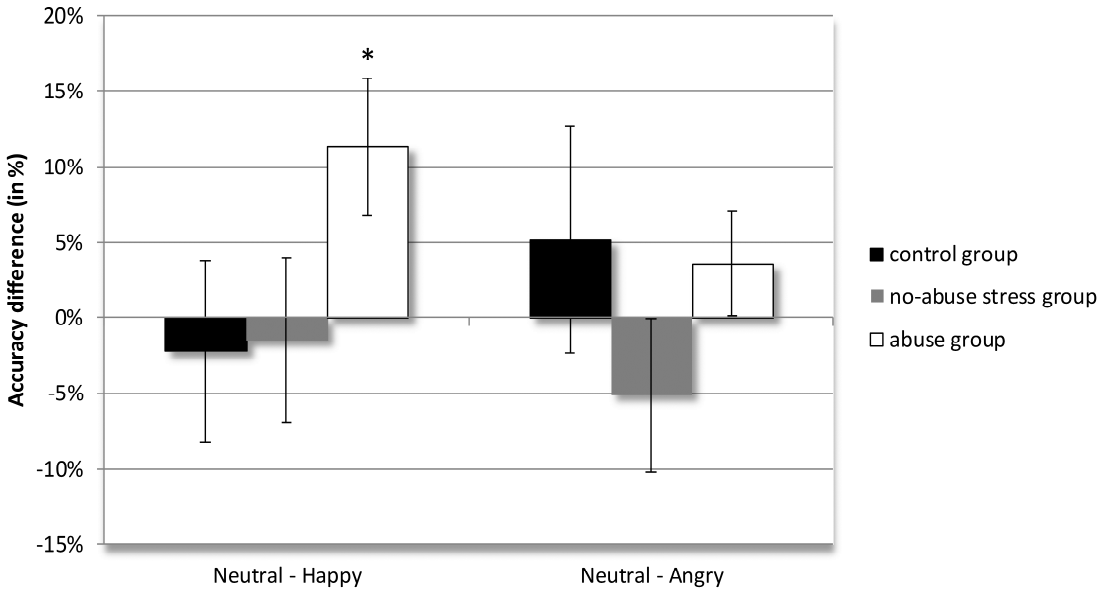

Figure 3. Accuracy difference scores (%) for the Miss1 condition in both the abuse and control group. Positive scores indicate a higher accuracy for neutral faces compared to either happy (left panel) or angry (right panel) faces. The figure illustrates the decreased accuracy for happy compared to neutral faces (in the Miss1 condition) in the abuse group. Error bars denote SEM. Asterisk indicates significance, $p < .05$

Reaction time

Reaction time analysis only yielded a main effect of location, $F(3, 147) = 16.17$, $p < .001$, partial $\eta^2 = .25$. Pairwise comparisons showed that participants were faster for match trials than for Miss1 ($p < .001$) and Miss2 ($p < .001$) trials. They were also faster for easier to perform Miss3 trials than for relatively more difficult Miss1 ($p < .001$) and Miss2 ($p = .002$) trials. The three-way interaction was not significant but approached conventional levels of significance, $F(12, 294) = 1.60$, $p = .09$, partial $\eta^2 = .06$ (Figure 2B). No other main effects or interactions were significant (Table 3).

Exploratory analyses of abuse type, duration, onset, and psychopathology

Because total psychopathology scores were higher in the stress and abuse compared to the control group, we investigated whether the accuracy difference that was found between the happy and neutral faces in the Miss1 condition was due to behaviour problems. The [Neutral - Happy] accuracy difference was not significantly correlated with the Total Psychopathology score (ASR), nor did it differ between participants who scored in the (sub)clinical range and participants with scores in the normal range. When looking at the abuse, stress and control group separately, no

Table 3.
Means and standard deviations of reaction times (in ms) and accuracy (in % correct) for the control, stress, and abuse group.

	Control group (n = 17)		Stress group (n = 17)		Abuse group (n = 21)	
	Mean RT (SD)	Mean Acc (SD)	Mean RT (SD)	Mean Acc (SD)	Mean RT (SD)	Mean Acc (SD)
Angry Match	791 (216)	87 (13)	740 (121)	82 (14)	807 (122)	87(12)
Happy Match	796 (117)	88 (11)	748 (118)	83 (12)	753 (99)	88 (11)
Neutral Match	785 (127)	86 (11)	772 (122)	80 (14)	774 (126)	86 (13)
Angry Miss1	861 (141)	54 (25)	821 (155)	61 (23)	848 (136)	60 (17)
Happy Miss1	864 (107)	61 (23)	800 (126)	57 (23)	918 (173)	52 (21)
Neutral Miss1	872 (129)	59 (16)	787 (122)	56 (19)	844 (98)	64 (19)
Angry Miss2	840 (149)	75 (18)	767 (148)	69 (25)	830 (101)	76 (14)
Happy Miss2	846 (135)	75 (19)	750 (122)	76 (20)	859 (98)	71 (19)
Neutral Miss2	834 (134)	76 (17)	746 (91)	72 (21)	848 (131)	75 (14)
Angry Miss3	805 (124)	87 (10)	712 (86)	85(16)	810 (114)	86 (15)
Happy Miss3	775 (125)	82 (16)	770 (120)	76 (16)	817 (107)	86 (16)
Neutral Miss3	813 (105)	84 (18)	750 (138)	83 (15)	825 (118)	85 (15)

RT = reaction time
Acc = accuracy
SD = standard deviations

significant correlations were found between the [Neutral - Happy] accuracy difference and the Total score, and Internalizing or Externalizing subscales in either group (all $p > .05$).

Additionally, we tested the association between the [Neutral - Happy] accuracy difference and details of the abuse, but no significant correlations were found with age of onset, duration, or frequency of abuse.. We also explored whether adding age of onset, duration, and frequency of abuse as covariates had any impact on the three-way Location by Emotion by Group interaction in the abuse group. However, the three-way interaction was still significant, $F(6, 90) = 2.21$, $p = .049$, partial $\eta^2 = .13$, suggesting little impact of abuse details on the main finding. Moreover, details of the abuse experience did not significantly interact with the factors Location and Emotion.

DISCUSSION

The present study sought to provide evidence for the persistent influence of childhood maltreatment on neuropsychological functions later in life. To this goal, the influence of emotional distraction on working memory, a function implicated in emotion regulation and emotion control (Joormann & D'Avanzato, 2010; Joormann & Gotlib, 2008, 2010; Schmeichel & Demaree, 2010; Schmeichel et al., 2008) was assessed in female survivors of childhood trauma (physical and/or sexual abuse) or experience of non-abuse related childhood stress. Two main findings pertinent to the study goal emerged. First, as hypothesized, affective valence interrupted effective working memory performance in female university students with a history of abuse. However, contrary to the hypotheses, this interruption only occurred for positive but not negative faces. Second, no interference effect was found for participants without a history of abuse or participants with non-abuse related childhood stress.

While much previous research has documented perturbed processing of, and heightened sensitivity to, negative emotional faces in individuals with a history of abuse (Gibb, Schofield, & Coles, 2009; Masten et al., 2008; Tottenham et al., 2011), findings of effects of positive emotion on cognitive performance in this population are scarce. Indeed, the main finding of the current study demonstrated impaired working memory

performance during positive faces in women with a history of abuse relative to women with non-abuse related childhood stress or women without childhood stress. Such data suggest a detrimental impact of incidental (i.e., irrelevant) positive information on working memory accuracy. Of note, this detrimental impact was only apparent in the most difficult distractor condition (close proximity between target and distractor) but not in easier to perform distractor conditions. On the easier working memory conditions, all groups performed equally well and were insensitive to distracting affective information. Although two recent neurobiological studies failed to find differential amygdala activation for happy compared to neutral faces in relation to childhood trauma (Dannlowski et al., 2012; van Harmelen et al., 2013), these studies did not take the relationship between emotional valence and skills subserving emotion regulation into account. An interesting study by Tottenham et al. (2011) that examined the influence of amygdala activity for fearful compared to neutral faces during inhibitory control in previously institutionalized children did unfortunately not examine happy faces. However, parallel research in reward processing has documented reduced reward sensitivity in individuals with a history of abuse (Guyer et al., 2006), also failing to elevate inhibitory control performance (Mueller et al., 2012). Thus, a question for future work concerns the implications of reduced processing of positive emotion for cognitive and emotion control after ES.

Based on evidence in individuals with depression or anxiety (Epp et al., 2012; Kerestes et al., 2012; Levens & Gotlib, 2010; Visu-Petra et al., 2010) and research on emotion processing in ES (Maheu et al., 2010; Masten et al., 2008; Tottenham et al., 2011), we also expected to find an effect in negative faces. However, negative incidental emotion did not seem to impair working memory in any group. One interesting theoretical conjecture regarding the selective effect of positive stimuli could be linked to resilience. All participants in the current study were university students, thus potentially showing a selectivity bias of individuals being able to attend university despite the early trauma. Such a notion would be supported by the idea that positive emotions aid high-resilient individuals to recover from stress (Ong, Bergeman, Bisconti, & Wallace, 2006) and enhance coping resources (Tugade, Fredrickson, & Feldman Barrett (2004). High resilience also moderates depression scores in maltreated individuals (Wingo et al., 2010) supported by psychophysiological data, which shows

that hemispheric asymmetry in the EEG distinguished between resilient and non-resilient children (Curtis & Cicchetti, 2007). Thus, given that there were no significant differences between the three groups of the current study on measures of resilience, it is conceivable that a selective effect of positive emotion might be limited to high resilient relative to low resilient individuals. However, as we had no a priori expectations with regard to this measure, current work in our laboratory is following-up on this intriguing possibility.

An alternative explanation for the lack of a difference between angry and neutral faces might be differences in interpretation of neutral and negative faces in affected and comparison participants. Previous studies have found that neutral faces are not always perceived as emotionally neutral in individuals with, or at-risk for, psychopathology. Masten et al. (2008) used a morphed facial identification task to examine processing of facial emotions in maltreated children. Compared to controls, maltreated children (with and without Posttraumatic stress disorder) showed a heightened ability to identify fearful faces when they were morphed with neutral faces (50% neutral, 50% fearful). Additionally, depression-prone individuals misinterpret neutral faces as being sad more often than healthy controls (Leppanen, Milders, Bell, Terriere, & Hietanen, 2004). In the current study, participants in the abuse and stress group reported more depressive symptoms than healthy comparisons, which could suggest that a negative interpretation bias might increase elaboration of neutral faces and consequently improve working memory performance for neutral and negative faces together. More work on distinguishing between these possibilities is required.

As alluded to earlier, cognitive biases have been implicated in several psychopathological disorders, such as depression or anxiety disorders. For example, depression is associated with interpretation biases towards negative stimuli (Gotlib et al., 2004; Joormann & Gotlib, 2008; Levens & Gotlib, 2010), with an increased interest in therapies targeting such biases (Baert, De Raedt, Schacht, & Koster, 2010; Beard, Sawyer, & Hofmann, 2012; Britton et al., 2013; Schweizer & Dalgleish, 2011; Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). A recent study on the effect of emotional working memory training in a healthy population yielded promising results, since the training improved not only performance on the emotional working memory task but also on a transfer task measuring emotional regulation capacity (Schweizer et al., 2013).

In addition, Pe et al. (2013) found beneficial effects on well-being when positive material was updated in working memory. Future research could examine the effectiveness of bias training when training either positive or negative information in individuals with a history of abuse.

Some limitations of the present study require discussion. One limitation certainly concerns the small sample size, even though a gradual effect of location distance on accuracy and sensitivity to incidental emotion suggests that the study group was sensitive to the task. However, due to the small sample size, the additional correlational analyses relating the [Neutral - Happy] accuracy difference in Miss1 trials to questionnaire results and details of abuse history should be considered exploratory. Secondly, while restricting the study to female participants might limit generalizability to men with a history of childhood abuse, it also constitutes a strength by excluding any possible confound of sex. A third limitation concerns the use of self-report measures. Even though the SLESQ is a well-validated instrument (Goodman et al., 1998; Green, Chung, Daroowalla, Kaltman, & DeBenedictis, 2006), we cannot exclude the possibility of recall bias. For the assessment of psychopathology, we also used a self-report measure, i.e. the ASR (Achenbach & Rescorla, 2003) , instead of a structured psychiatric interview. However, the emphasis of the current study was on the experience of abuse on cognitive mechanisms of emotional processing rather than clinical psychopathology. In addition, the ASR is a reliable and valid (Achenbach & Rescorla, 2003) instrument and is frequently used to assess psychopathology in young adults (Hack et al., 2004; Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2010). Moreover, it detected significant differences between the two groups in experienced pathology on several scales of the ASR. Finally, because of time constraints and in order to avoid fatigue in participants, we decided to only use one positive and one negative emotional expression in the task. Even though sad faces are often used in depression research, we opted for angry faces given the heightened sensitivity of traumatized individuals to threatening information (Gibb et al., 2009; Johnson, Gibb, & McGeary, 2010; Pine et al., 2005; Pollak & Tolley-Schell, 2003). Future work could examine sensitivity to other emotional expressions.

Conclusion

The present study highlights interfering effects of positive emotion on working memory performance in women with a history of abuse relative to women with other childhood stressors or comparisons without a history of ES. These findings aim to increase awareness of history of abuse among female university students and the impact it might have on cognitive skills related to emotion control. Larger and more strongly powered studies are needed to replicate this finding to investigate how individual differences and abuse characteristics influence working memory impairment for positive information.

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CHAPTER 6

GENERAL DISCUSSION

RECAPITULATION OF THE RESEARCH GOALS

The general aim of this doctoral dissertation was to investigate working memory (WM) for relevant and irrelevant emotional information in healthy adolescents and adults. Several theories on neurobiological development have emphasized the imbalance between cognitive control and emotional processing networks in the adolescent brain as a possible explanation for the typical behavioural patterns observed during this life phase (Ernst, Pine, & Hardin, 2006; Somerville & Casey, 2010; Steinberg, 2008). Examples of these typical behaviours include a propensity for risk-taking and increased mood instability. The studies that are reported in this thesis were designed to shed light on how emotion impacts WM during adolescence, since this is a crucial cognitive control skill known to develop relatively late compared to other cognitive control abilities (Luna, Garver, Urban, Lazar, & Sweeney, 2004). Furthermore, deficits in (emotional) WM have been related to ineffective emotion regulation strategies, for example rumination (De Lissnyder, Koster, & De Raedt, 2012; Demeyer, De Lissnyder, Koster, & De Raedt, 2012). Investigating these processes in healthy adolescents could thus provide clues about the development of depression in this age group.

Even though studies on emotional WM in a developmental sample are very scarce, during the last decade this topic has received increased attention in the adult literature. Many paradigms have been developed to investigate interactions between affective and cognitive processes. To get an overview of these studies and to summarize

the findings, this thesis started with a meta-analysis that identified brain regions consistently implicated in studies using an emotional manipulation (e.g. mood induction, emotional pictures or faces, reward) within a cognitive control context (**Chapter 2**). Then, based on the adult literature, we selected an experimental paradigm that was suitable both for adults and adolescents, namely the emotional n-back task. Variants of this task have already been used in adolescent and adults, both in healthy and psychopathological samples (Ladouceur et al., 2005; Ladouceur et al., 2009; Levens & Gotlib, 2010). But even though these paradigms are all "emotional n-back tasks", there is quite some variety in their designs. For example, in the studies reported by Levens and Gotlib (2010, 2012), emotional faces are presented centrally and participants are asked to remember and compare the valence of the faces. Ladouceur and colleagues (Ladouceur et al., 2005; Ladouceur et al., 2013; Ladouceur et al., 2009), on the other hand, aim to investigate the impact of emotional distractors on WM and thus present emotional faces as flankers during a letter n-back task. In our studies, we wanted to compare the influence of emotional faces on WM when the emotional expression is relevant for the WM task versus when it is not relevant and thus distracting. In **Chapter 3**, we first tested whether adolescents and adults differed in their behavioural performance on this task. Next, we explored the neural correlates of this task with fMRI (**Chapter 4**). For the analysis of these fMRI results, we focused specifically on the regions that were identified in the meta-analysis of emotion-cognition interactions in adults (**Chapter 2**). In a final study, we inquired how traumatic events during childhood or adolescence (such as sexual or physical abuse, the death of close family member or a life-threatening illness) might alter the way in which emotional stimuli impact WM processing (**Chapter 5**). For this study, we used a new paradigm tapping into spatial WM processes.

MAIN FINDINGS

1. Behavioural results

1.1 The impact of relevance on emotional effects in working memory

Studies investigating the impact of emotional stimuli on cognitive control skills have yielded mixed findings. While some report behavioural improvements for emotional versus neutral stimuli (Kanske & Kotz, 2011; Levens & Phelps, 2008), others indicate that emotional stimuli can have detrimental effects on cognitive control processing (Blair et al., 2007; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos & McCarthy, 2006). In this thesis, we investigated whether the relevance of emotional stimuli could offer an explanation for this diverging evidence. In our behavioural study using the emotional n-back task in healthy adolescents and adults (**Chapter 3**), we indeed found performance to be affected by the relevance of the emotional stimuli. More specifically, RTs but not accuracy differed depending on whether participants had to remember the emotional expression of the faces that were presented (*valence task*), or whether attention was directed at a non-emotional feature, i.e. the gender of the face (*gender task*). In the valence task, both adults and adolescents were faster for happy compared to neutral and angry faces. Furthermore, this behavioural effect was replicated in the fMRI study reported in **Chapter 4**. Findings in the gender task, on the other hand, did not show consistent effects across studies. Whereas happy faces were found to be associated with slower responses in adolescents but not adults in the behavioural study (**Chapter 3**), both age groups responded slower when angry faces were shown compared to happy or neutral faces in the fMRI study (**Chapter 4**). Thus, even though these studies clearly indicate that relevance is an important factor when considering the impact of emotional stimuli on WM, the direction of this effect was not consistent for irrelevant stimuli. Furthermore, although a consistent effect was found for relevant emotional stimuli in our studies using the emotional n-back task, it is uncertain whether this effect translates to other tasks and/or other cognitive control skills. However, one recent study (Schel & Crone, 2013) has examined the impact of

relevant and irrelevant emotions on response inhibition across a sample of 6- to 25-year old participants. In this task, relevant happy faces resulted in faster RTs and higher accuracies on go trials, and in fewer false alarms on no go trials, compared to fearful faces. When the expression of the face was made irrelevant, by asking participants to respond to the color of the face, there was no effect of the emotional manipulation on response inhibition. Thus, while the impact of irrelevant emotional stimuli differed from our findings, the effects in the relevant emotional context replicate the findings from our behavioural and fMRI study on emotional WM, with happy faces resulting in better performance. In the next two sections, we will discuss the findings in both attention conditions separately in more detail.

1.2 The influence of relevant emotional stimuli on working memory: always look on the bright side of life

As mentioned in the previous section, we consistently found a performance improvement for relevant happy faces across studies (**Chapter 3 and 4**) and age groups (adolescents and adults). This 'positivity effect' has also been reported in adults by Levens and Gotlib (2010) using a similar face n-back task where participants were asked to remember and compare the emotional expression that was shown. In healthy adults, reaction times for happy faces were faster both in the 0-back and the 2-back task. They suggested that this benefit for happy faces in WM reflects a bias to maintain positive information, which might underlie resilience. Similar biases for positive information in healthy adults have also been found in other domains, such as attentional research (Joormann & Gotlib, 2007; Sanchez, Vazquez, Marker, LeMoult, & Joormann, 2013) and word processing (Herbert, Kissler, Junghofer, Peyk, & Rockstroh, 2006; Kuchinke et al., 2005).

In adolescents, only one study, to our knowledge, has used an n-back task with relevant emotional stimuli (Passarotti, Sweeney, & Pavuluri, 2010). However, this study aimed to compare performance of adolescents with bipolar disorder (BD) or attention-deficit hyperactivity disorder (ADHD) to healthy control subjects. In keeping with this, a separate behavioural analysis in healthy controls was not reported. Nevertheless, a main effect of emotion on RT was reported across groups, with slower RTs for angry

compared to neutral faces, and no significant differences with happy faces. This absence of a positivity effect could be due to differences in task design. In our study, as well as in the study reported by Levens and Gotlib (2010), faces only matched in emotional expression and not face identity, whereas a match in expression was always accompanied by a match in face identity in the study by Passarotti et al. (2010). Therefore, it is possible that participants focused more on the encoding of face identity, thus limiting the processing of the emotional valence of the face, and consequently limiting its impact on WM performance.

Even though the impact of relevant emotional stimuli on WM has been largely understudied in developmental samples, there are a few studies that have investigated the impact on another cognitive control skill, i.e. inhibitory control. For example, Hare et al. (2008) used an emotional go/no-go paradigm in children (7-12 years), adolescents (13-18 years) and adults (19-32 years) to assess inhibition for relevant emotional faces. In each block, participants saw two emotional expressions (fearful, happy or neutral faces) and were asked to respond to one of these faces, while withholding their response when confronted with another face. All three age groups were found to be faster in response to happy faces, and this effect was replicated in two other independent studies (Schel & Crone, 2013; Somerville, Hare, & Casey, 2011).

Thus, this consistent bias towards happy faces that we identified across studies is supported by both the adult and adolescent literature. Happy faces seem to attract attention more easily than other emotional expressions, at least in healthy participants, and this attentional capture can influence both the ability to inhibit responses but also WM processes. Indeed, increasing evidence using attentional blink (Miyazawa & Iwasaki, 2010) and visual search tasks such as the face-in-the-crowd paradigm (Becker, Anderson, Mortensen, Neufeld, & Neel, 2011; Juth, Lundqvist, Karlsson, & Ohman, 2005) points to an attentional preference for happy faces in healthy participants. Whereas early research on attention for facial expressions reported a faster detection of angry faces within a crowd of neutral or emotional distractor faces (Hansen & Hansen, 1988), this so called ‘anger superiority effect’ has been challenged (Coelho, Cloete, & Wallis, 2010; Purcell, Stewart, & Skov, 1996). As a recent study suggested (Craig, Becker, & Lipp, 2014), more and more evidence is found for a ‘happiness superiority effect’ when using pictures of human faces (Becker et al., 2011; Byrne &

Eysenck, 1995; Juth et al., 2005; Williams, Moss, Bradshaw, & Mattingley, 2005) instead of schematic facial stimuli (Eastwood, Smilek, & Merikle, 2001; Fox et al., 2000; Ohman, Lundqvist, & Esteves, 2001; Tipples, Young, Quinlan, Broks, & Ellis, 2002).

Why would humans be more attentive to happy faces? Why is attention more easily attracted towards happy faces? One explanation pertains to low-level perceptual features that are related to emotional faces (e.g. complexity of the face, shape of the eyebrows, shape of the mouth). To investigate whether perceptual features may explain the 'happiness superiority effect' in visual search tasks, Becker et al. (2011) carefully designed a series of experiments to rule out the effect of such perceptual factors. Even when controlling for low-level visual confounds, these authors still found evidence for an advantage of happy faces, i.e. higher accuracies and faster RTs. In sum, this study indicated that the emotional valence that is conveyed by a happy face influences performance above and beyond perceptual features that characterize smiling faces, such as the V-shape of the mouth.

The question thus remains: why would happy faces attract more attention? One possibility is that this is due to heightened familiarity with happy faces, making these faces easier to process and leading to better encoding (Baudouin, Gilibert, Sansone, & Tiberghien, 2000). Although one could argue whether people are most often confronted with happy or neutral faces in daily life. Another explanation for the 'happy superiority effect' is that happy faces can be seen as rewarding. Indeed, a recent study comparing the influence of monetary and social reward, i.e. happy faces, in children supports this notion (Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009). These children (age 8-12) performed a go/no-go task paired with social reward, monetary reward, a combination of both, or no reward at all. Results indicated that both social and monetary reward significantly improved performance on the go/no-go task, albeit stronger effects were found for monetary reward. Similar findings have been reported in adults using a social variant of the 'monetary incentive delay' (MID) task (Spreckelmeyer et al., 2009). In the classical MID task (Knutson, Westdorp, Kaiser, & Hommer, 2000) participants are first presented with a cue representing a potential reward, followed by a target stimulus. If their response to this target is fast enough, participants are offered the reward. Levels of potential reward are usually manipulated and are represented by different cues. In the social variant of this task, the social

incentive delay (SID) task , the reward consisted of a smiling face. Although responses were generally faster in the MID task, a significant RT improvement in comparison to the no-reward condition was found in both tasks. Importantly, neural activation in the reward system (e.g. the nucleus accumbens) was increased for both types of reward during the anticipation phase. In sum, these studies (Kohls et al., 2009; Spreckelmeyer et al., 2009) provide evidence for a rewarding effect of happy faces.

Interestingly, in the behavioural study discussed in **Chapter 3**, the performance improvement for happy faces in the valence task was slightly larger in adolescents compared to adults, although this trend failed to reach significance. These data suggest that the rewarding effect of happy faces is more pronounced in adolescents than adults. This idea is also in line with predictions from neurobiological models of adolescent behavior (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), positing increased sensitivity to emotional – especially rewarding – stimuli.

Evidently, given that the differential impact of happy faces in adolescent and adults was only trending, this effect should be interpreted with caution. Furthermore, using the same emotional n-back task in the scanner (**Chapter 4**), we found that the WM improvement for relevant happy faces was similar in adolescents and adults, thus failing to replicate the trend reported in the behavioural n-back study (**Chapter 3**). This failure could be due to power issues related to the smaller sample size, differences in task context (in the fMRI scanner versus in a quiet laboratory setting) or age group. Indeed, whereas adolescent participants in the behavioural study were between 12 and 14 years of age, the age range for adolescents in the fMRI study was broader, i.e. between 12 and 16 years of age. Similarly, adults also differed in age between the two studies, i.e. between 18 and 29 (M_{age} = 21.0) in the behavioural study and between 25 and 35 (M_{age} = 27.4) years of age in the fMRI study. Of course, this explanation remains speculative and future studies should include several age groups to investigate whether the developmental differences in emotional WM reported in the behavioural study can be replicated, and if so, which age range is most sensitive to happy faces.

1.3 The influence of irrelevant emotional stimuli on working memory

In the behavioural study using the emotional n-back task (**Chapter 3**), adolescents were found to respond slower when confronted with a happy compared to a neutral face in the gender task. In adults, on the other hand, none of the emotional expressions were found to impact performance. As discussed in the previous paragraph, happy faces are generally found to attract more attention, which is known as the 'happiness superiority effect' (Becker et al., 2011). The difference between adolescents and adults in this regard could be explained by dual-process theories of adolescent behaviour (Somerville & Casey, 2010; Steinberg, 2008), assuming an imbalance between affective and cognitive processing. Consequently, the slowing in reaction time in adolescents during the gender task can be due to 1) increased sensitivity for emotional stimuli, especially positive stimuli and 2) delayed development of cognitive control abilities.

A possible explanation for adolescents' heightened sensitivity to happy faces could be the increased saliency or biological relevance of these positive stimuli. Adolescence is a period when the social environment becomes more important. Unlike children who have more variable friendships, adolescents are focused on building stronger connections with peers, resulting in longer lasting friendships. As a consequence, social signals that possibly convey crucial information about these relationships, such as a smile from a peer, become increasingly important during adolescence. This heightened relevance of happy faces could underlie our finding of increased distractibility. During the emotional n-back task, adolescents' attentional resources might be mobilized to process the emotional information conveyed by the happy faces, thus limiting the attentional capacity that is available for the main task. This interpretation is consistent with a study by Ladouceur et al. (2005) showing that healthy adolescents were slower on a 0-back and 2-back WM task when the target stimuli were superimposed on positive compared to neutral background pictures. They suggested that greater attentional resources were allocated to processing the positive background picture even though this was irrelevant to the task goal. A similar mechanism might be at work in our emotional n-back task. Furthermore, the fact that happy faces were more distracting for adolescents could also be due to immature

cognitive control skills. That is, adolescents might have more difficulties reorienting their attention to task-relevant features.

However, the decrease in adolescents' performance in response to irrelevant happy faces must be interpreted with caution, since this effect could not be replicated in the fMRI study (**Chapter 4**), using the same emotional n-back task. In that study, slower reaction times for angry compared to happy and neutral faces were found in the gender task. As previously mentioned, even though both studies employed the same emotional n-back task, there were some methodological differences between them, i.e. experimental context and the age range of adolescent and adult participants that might have influenced performance on the task.

1.4 Individual differences and emotional working memory performance

Across studies (**Chapter 3-5**), no correlations were found between individual differences (based on self-report questionnaires) and performance measures. Measures that were included in all studies were depression questionnaires i.e. the Beck Depression Inventory for adults (BDI-II NL; Beck, Steer, Ball, & Ranieri, 1996; van der Does, 2002) and the Children's Depression Inventory for adolescents (CDI; Kovacs, 1992; Timbremont, Braet, & Roelofs, 2008), and anxiety questionnaires, i.e. the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) and State-Trait Anxiety Inventory for Children (STAI-C; Bakker, van Wieringen, van der Ploeg, & Spielberger, 2004; Spielberger, 1973). Previous studies have shown that individual differences, such as self-reported trait anxiety or depressive symptomatology, are related to performance on an emotional WM task (Joormann & Gotlib, 2008; Ladouceur et al., 2009; Levens & Gotlib, 2010, 2012; Pe, Raes, & Kuppens, 2013). For example, Ladouceur et al. (2009) reported that high anxious participants (8-30 years of age) responded slower on a 2-back memory task with fearful faces as distractors. Interestingly, this effect also interacted with age, indicating that this interference was more pronounced in younger participants (children and adolescents). Such modulation of WM performance by trait anxiety could not be identified in our empirical studies (**Chapter 3-5**). Furthermore, we also failed to show any correlations between scores on

depression questionnaires and performance measures. The absence of a relationship between RTs or accuracy on the one hand and depression or anxiety scores on the other hand could be due to the selection of participants. In **Chapter 3-5** participants were screened for psychopathology using the Adult Self Report (ASR; Achenbach & Rescorla, 2003) or the parent form of the Child Behaviour Checklist (CBCL; Achenbach & Rescorla, 2001). To ensure that only healthy adolescents and adults would participate, subjects scoring with the clinical range on this screening were excluded in **Chapter 3 and 4**. In the behavioural study in **Chapter 3**, however, only three (adolescent) participants were excluded due to scores in the clinical range on the Internalizing, Externalizing or Total Problems Scale of the ASR or CBCL, so it is unlikely that this explains the absence of correlations between individual differences in anxiety/depressive symptoms and performance measures. In **Chapter 4**, exclusion criteria were a clinical score on the ASR or CBCL, or a z-score higher than 2 on the STAI, STAI-C, BDI or CDI. Although these exclusion criteria ensured that both groups were equal in terms of depressive/anxiety symptoms, excluding these participants could have limited the variation in anxiety and depression scores, resulting in non-significant correlations. Furthermore, research reporting a relationship between depression and WM for emotional information have often compared depressed and non-depressed individuals (Joormann & Gotlib, 2008; Ladouceur et al., 2005; Levens & Gotlib, 2009, 2010), instead of correlating performance measures with scores on depression questionnaires. Thus, the effects found in these studies might be absent or less strong in healthy participants. In **Chapter 5**, participants scoring in the clinical range on the ASR or CBCL were not excluded. However, exploratory analyses indicated that the group difference that was found (accuracy difference of neutral - happy faces in the most difficult distractor condition, i.e. Miss1) did not correlate with scores on the psychopathology screening questionnaire (ASR). Additional exploratory analyses (not reported in **Chapter 5**) correlating this accuracy difference score with STAI trait and BDI scores also failed to find significant effects (all $p > .37$, Holm-corrected).

For exploratory reasons, the Behavioural Inhibition/Behavioural Activation System scales (BIS/BAS scales; Carver & White, 1994) were also administered in our studies comparing adolescents and adults (**Chapter 3 and 4**). As discussed in the general introduction, the triadic model (Ernst 2006) assumes an imbalance between a

regulatory system and two emotional-motivation systems, i.e. an approach-related and avoidance-related system. The latter distinction is based on the biopsychological personality theory of Gray (1970), who suggested that individual differences are determined by an approach-related Behavioural Activation System (BAS) and an avoidance-related Behavioural Inhibition System (BIS). Thus, in our studies the BIS/BAS scales were administered to examine whether our experimental effects could be driven by an imbalance between both systems. However, neither in the behavioural (**Chapter 3**) nor fMRI study (**Chapter 4**) did we find a correlation between scores on the BIS/BAS and performance measures.

A last measure of individual differences that was included in the fMRI study reported in **Chapter 4**, was the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988). Even though there is a high correlation between pubertal development and chronological age, there still exists a large variation in pubertal stage in adolescents within the same age range. Therefore, including measures of pubertal maturation allows researchers to disentangle the effects of both factors. In our study (**Chapter 4**), however, no significant correlations were found between PDS score and behavioural performance on the emotional WM task. Although the PDS is a useful tool to assess the level of pubertal development (Tanner stage) very quickly and without the need for clinical examination, correlations between physician Tanner ratings and self-reports on the PDS are rather modest, i.e. between .61 and .67 (Brooks-Gunn, Warren, Rosso, & Gargiulo, 1987). Thus, future studies should use other measures of pubertal development to disentangle the effects of chronological age and puberty.

1.5 Emotional working memory in an at-risk population

As discussed in the previous section, in our empirical studies (**Chapter 3-5**) we could not find significant correlations between individual difference measures, such as depressive symptomatology and trait anxiety, and behavioural performance on emotional WM tasks. A possible explanation for the absence of these relationships is that all participants in **Chapter 3 and 4** were healthy subjects, and participants scoring clinically on a psychopathology screening were excluded, thus limiting the variability. In **Chapter 5**, however, participants with high scores on psychopathology measures were

not excluded since this was a study in a non-clinical but at-risk population, i.e. adults reporting stressful events during childhood or adolescence. Previous studies have shown that experiencing such events impacts both emotional (Gibb, Schofield, & Coles, 2009; Maheu et al., 2010; Masten et al., 2008; Tottenham et al., 2010) and cognitive processing (De Bellis, Hooper, Spratt, & Woolley, 2009; Jovanovic et al., 2012; Majer, Nater, Lin, Capuron, & Reeves, 2010), as well as the interaction between both (Mueller et al., 2012; Mueller et al., 2010), and that it increases the chance of developing psychopathology (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001).

Although there were also no significant correlations between questionnaire measures, such as the BDI or STAI, and the accuracy difference scores (see previous section), we did find between-group differences on the emotional spatial WM task in students with a history of childhood sexual or physical abuse (abuse group) in comparison to students reporting other types of childhood stress (stress group), such as parental loss or witnessing violence, or students without early-life stress (control group). More specifically, women in the abuse group showed a deficit for (irrelevant) positive stimuli in the most difficult condition of a spatial emotional WM task, compared to the stress and control group, controlling for levels of depression and anxiety. This finding is in contrast to our hypotheses. Given that childhood trauma constitutes a risk factor for developing psychopathology, most commonly depressive and anxiety disorders (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001), and based on research in depressed and anxious populations reporting attentional and WM biases for negative stimuli (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Gotlib & Joormann, 2010; Mathews & MacLeod, 2005; Peckham, McHugh, & Otto, 2010), we expected to find an effect of angry and not happy faces.

Given the paucity of data on the processing of positive stimuli in abused individuals, the mechanism behind this deficit for happy faces is unclear. A possible explanation could be that abused individuals exhibit less efficient encoding of positive stimuli such as happy faces, thus leading to worse performance during retrieval. The finding that emotional effects were only evident in the most difficult condition could be due to a ceiling effect in the other conditions. Another possible interpretation is that abused individuals' attention might be more easily captured by the positive valence of the faces, hindering processing of other stimulus features, such as the location of the

face. Such increased attention towards happy faces in adults reporting a history of childhood abuse has also been found in a recent study using a dot-probe task with angry and happy faces (Fani et al., 2012). Since biases towards positive stimuli are usually considered adaptive (Joormann & Gotlib, 2007) and have been linked to emotional well-being (Pe, Koval, & Kuppens, 2013), this finding is counterintuitive. However, in the study by Fani et al. (2012), a bias towards happy faces was associated with post-traumatic stress disorder (PTSD) symptoms, suggesting that this mechanism could play a role in the maintenance of PTSD. According to the authors, excessive attention to positive cues is related to avoidance of threat-related signals, thus preventing extinction of the fear associated with these cues and contributing to the maintenance of PTSD. Of course, such interpretations remain speculative and more studies are needed to examine the exact role of a bias towards positive stimuli in individuals reporting childhood stress or trauma.

2. Neurobiological findings

2.1 Neural correlates of emotion cognition interactions in adults

As is evident from the previous sections, emotional stimuli have an impact on WM performance both in adolescents and adults. A question that has intrigued many researchers in the last decade, however, is how such emotion-cognition interactions are represented in the brain. Although many recent studies have looked at the interplay between affective processing on the one hand and cognitive control processes (inhibition, WM or task switching) on the other hand in adults (Dolcos et al., 2008; Dolcos & McCarthy, 2006; Mohanty et al., 2005; Sagaspe, Schwartz, & Vuilleumier, 2011), these findings had not yet been integrated. Therefore, in **Chapter 2** we set out to examine which brain regions are consistently activated during cognitive control tasks within an emotional context, by means of the Activation Likelihood Estimation (ALE) method. This meta-analysis revealed several brain regions (see Table 2, **Chapter 2**), including clusters in the prefrontal cortex (right dorsolateral prefrontal cortex, bilateral inferior frontal gyrus, superior/medial frontal gyrus), parietal cortex (inferior parietal lobule), and subcortical areas (amygdala, anterior insula).

An important contribution of this study is that it provides a more detailed account of regions that are important in integrating cognition and emotion. In the literature, some models have been proposed but due to their theoretical nature, they are generally rather vague about the precise anatomical locations of important 'hubs'. For example, Pessoa (2008) proposed a cognitive-affective control circuit, comprising the lateral PFC, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala and nucleus accumbens. The meta-analysis reported in **Chapter 2** partially supports this model, with important clusters being located in the lateral PFC, ACC and amygdala, but not in the nucleus accumbens or orbitofrontal cortex. However, the absence of the nucleus accumbens could be due to the affective manipulations of the studies included in the meta-analysis, with most studies using IAPS pictures, faces or words instead of reward, which has consistently been shown to activate the nucleus accumbens (Ikemoto & Panksepp, 1999; Knutson, Adams, Fong, & Hommer, 2001). Importantly, we did identify a cluster in the right amygdala and several clusters in the lateral PFC and ACC. More specifically, within the lateral PFC, clusters were found in the right dorsolateral prefrontal cortex (DLPFC) and bilateral inferior frontal junction (IFJ). These regions are thought to be involved in the maintenance (DLPFC) and updating (IFJ) of task representations in WM (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005; Miller & Cohen, 2001).

Our findings indicate that in the presence of emotional information activation in these regions is increased. In right DLPFC, activity was also higher when emotional stimuli were task irrelevant, which might reflect the need to allocate processing resources to task-relevant stimuli. Within the ACC, the subgenual part seems to play an important role in emotion-cognition interactions. Previous accounts have divided the anterior cingulate cortex into a dorsal, cognitive, and ventral, affective, division (Bush 2000). Following this distinction, the ventral part of the ACC (including the subgenual ACC) has been suggested to be involved in regulating activity in limbic regions that are crucial for emotional processing, such as the amygdala (Etkin, Egner, & Kalisch, 2011; Matthews et al., 2009).

Apart from delivering a more specific and detailed view of frontal regions involved in emotion-cognition interactions, another major contribution of the meta-analysis concerns the empirical evidence for the involvement of parietal cortex, anterior

insula, and even occipital cortex. The anterior insular cortex is tightly linked to limbic regions (Craig, 2009) and is implicated in interoceptive awareness and the detection of (emotional) salience (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Furthermore, recent accounts have suggested that this region is involved in switching between attentional networks (i.e. a central-executive network involving the DLPFC, and a default mode network involving ventromedial PFC) in case a salient event is detected (Menon & Uddin, 2010). Such attentional reorienting is executed via connections with parietal cortex (Uddin et al., 2010), which might also influence processing in occipital cortex (e.g. fusiform gyrus). It is important to note that these interpretations remain speculative, given that the meta-analysis data only provides evidence for regions involved in emotion-cognition interactions and not for their functional contribution. Future research is therefore needed to investigate the role of each region and to elucidate how they are integrated. Nevertheless, the meta-analysis can be helpful in this regard by facilitating the generation of hypotheses.

2.2 Neural correlates of emotional working memory: a developmental perspective

2.2.1 Overview of the main findings

In **Chapter 4**, the clusters that were identified in the meta-analysis were used as regions of interest in an fMRI study. The goal of this study was to compare the neural correlates of the emotional 0-back/2-back task in adolescents and adults. Based on previous evidence and neurobiological theories assuming a mismatch between emotional and cognitive processing in adolescents (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), we hypothesized to find developmental differences in (pre)frontal cortex and limbic regions. Results indeed showed that compared to adults, adolescents had lower activation levels in several frontal clusters, such as the IFJ, DLPFC and superior/medial frontal gyrus. Furthermore, activity in these regions was related to performance in adults, but not in adolescents. This finding suggests that adolescents rely less on activation in these frontal regions to perform the emotional n-back task, which is consistent with the idea that activation shifts from a diffuse to focal activation during development (Bunge & Wright, 2007; Crone, 2009; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Klingberg, Forssberg, & Westerberg, 2002). Compared

to adolescents, adults also increasingly activated other areas (e.g. the fusiform gyrus and inferior parietal lobule) that were critical for task performance, as evidenced by their positive correlations with accuracy scores. This further supports the idea that the network underlying WM performance in adults is still immature and continues to develop during adolescence.

Furthermore, while activity in two frontal regions was influenced by the emotional faces that were shown throughout the task in adults, this was not the case in adolescents. Both right DLPFC and left inferior frontal gyrus (IFG) were increasingly activated in response to angry compared to happy or neutral faces in adults, but not in adolescents. Additional recruitment of the right DLPFC when confronted with angry faces could reflect its role in maintaining attentional set in the presence of salient, emotional information (Banich et al., 2009; Blasi et al., 2007; Dolcos et al., 2008). Left IFG, on the other hand, might be implicated in diminishing the effects of emotional stimuli on higher-order cognitive processes by inhibiting or suppressing activation in affective regions, such as the amygdala (Anticevic, Repovs, & Barch, 2010; Dolcos & McCarthy, 2006; Mincic, 2010).

Developmental differences were also found in bilateral amygdala. Adolescents activated left amygdala more strongly when confronted with angry compared to happy or neutral faces in the gender task, which could indicate stronger distraction by emotional information (Anticevic et al., 2010; Dolcos et al., 2008; Dolcos & McCarthy, 2006). In right amygdala, only cognitive load had an impact on activation levels, with more activity for the 2-back compared to the 0-back condition in adolescents than adults. This could be due to immature top-down control over amygdala functioning in adolescents (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008).

Unexpectedly, activation in the left and right amygdala depended on different experimental factors. In the literature, many theories have been proposed for a lateralization in the amygdala, depending on valence (Sackeim et al., 1982), sex (Hamann, 2005; Killgore & Yurgelun-Todd, 2001), stimulus type (Markowitsch, 1998; Phelps et al., 2001) or temporal dynamics (Glascher & Adolphs, 2003; Wright et al., 2003). A recent meta-analysis (Sergerie, Chochol, & Armony, 2008) failed to find lateralization effects in the amygdala as a function of sex or valence, but confirmed the importance of stimulus type and temporal dynamics. Amygdala responses were

stronger for faces compared to pictures or words, both for positive as well as negative stimuli. Furthermore, activation was more often found in the left than the right amygdala. In our study, however, both age groups activated the right amygdala more strongly during the 0-back compared to the 2-back task (although this effect was stronger in adult than adolescents). Furthermore, within the 0-back task, happy and angry faces resulted in more activation than neutral faces, confirming the finding by Sergerie et al. (2008) that both positive and negative emotional expressions can modulate amygdala responses. In the left amygdala, on the other hand, only adolescents seemed sensitive to our manipulations. Given these developmental differences, it would be interesting for future studies on amygdala functioning and lateralization to also include age as a factor in the analysis.

2.2.2 Implications for neurobiological theories of adolescent behaviour

In general, our findings seem to support the claims made by neurobiological theories of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), i.e. prefrontal hypoactivation and limbic hyperactivation. As discussed in the previous section, activity during the emotional n-back task was increased in several prefrontal regions in adults compared to adolescents. However, our results indicated that developmental differences were not restricted to the ventrolateral/medial prefrontal cortex, as suggested by the triadic model. Instead, adults activated the inferior parietal lobule, fusiform gyrus, insula, precuneus and DLPFC to a larger extent than adolescents, and activation in right DLPFC and left IFG differed depending on the emotional expression of the faces in adults, while no differences were found in adolescents. The latter possibly reflects immature prefrontal top-down regulation of hyperactive subcortical regions, as suggested by Hare et al. (2008). In that study, children, adolescent and adults performed an emotional go/no-go task while undergoing fMRI. Findings indicated exaggerated amygdala activity in adolescents compared to adults and children, and habituation of this response was related to functional connectivity between ventral PFC and the amygdala. In our study, one cluster in ventral PFC, i.e. left IFG, was increasingly activated in response to angry compared to neutral faces in adults but not adolescents. Left IFG could thus play a role in controlling the impact of emotional stimuli on the WM task (Anticevic et al., 2010;

Dolcos & McCarthy, 2006; Hare et al., 2008; Mincic, 2010). Furthermore, a similar effect of the emotional manipulation in DLPFC in adults but not adolescents suggests that this region is equally important and should thus be included in future versions of the triadic model.

Findings in the amygdala were in line with neurobiological theories (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), with generally more activation in adolescents than adults, although the exact results in left and right amygdala differed (see discussion in section 2.1.1). Based on the triadic model, however, we had hypothesized to find activation differences in ventral striatum (VS) for happy compared to neutral faces in both adults and adolescents, although stronger effects were expected in the latter group. This would be consistent with the idea that happy faces serve as a reward (Kohls et al., 2009; Spreckelmeyer et al., 2009), especially for adolescents who are thought to be more sensitive to social cues (Guyer, Choate, Pine, & Nelson, 2012; Jones et al., 2011; Somerville et al., 2013). However, no emotion or group effects were found in VS, suggesting that the behavioural improvement in response to happy faces in our fMRI study was not due to its rewarding properties. Previous studies in adults are inconclusive in this regard, with only one study reporting higher VS activity in response to happy compared to neutral faces in the context of a go/no-go task (Somerville et al., 2011). Unfortunately, Hare et al. (2008) did not include VS as an ROI in their study, limiting the available evidence for VS involvement in the processing of happy faces in adolescents. More studies are therefore needed to clarify this issue, for example by directly comparing the effect of reward and happy faces on VS activity in an adolescent sample, compared to both adults and children.

2.2.3 Individual differences and neural correlates of emotional working memory

In contrast to our expectations, we failed to find significant correlations between neural activation in the ROIs, for example in the amygdala, and individual difference measures, such as anxiety and depressive symptoms. This is inconsistent with previous studies reporting a relationship between anxiety levels and amygdala responses to negative - especially fearful - faces both in healthy adolescents (Hare et al., 2008; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004) and adults (Etkin et al., 2004), but also when comparing patients with anxiety disorders to healthy controls

(Evans et al., 2008; McClure et al., 2007; Monk, Telzer, et al., 2008; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Thomas et al., 2001). Studies in youth as well as adults at risk for or suffering from major depressive disorder have also indicated abnormalities in amygdala functioning compared to healthy controls (Drevets, Price, & Furey, 2008; Monk, Klein, et al., 2008; Roberson-Nay et al., 2006; Surguladze et al., 2005; Thomas et al., 2001), although the direction of the effect is less clear as in anxious populations. Besides changes in amygdala activation, depressive patients have also shown aberrant responses in VS, especially with regard to the processing of happy faces (Epstein et al., 2006; Monk, Klein, et al., 2008). Based on these findings, we had expected to find correlations between amygdala and VS activity on the one hand and anxiety or depressive symptoms on the other hand. As noted in section 1.4, the absence of such an effect could be due to the exclusion of participants scoring clinically on the ASR, CBCL, STAI (C) Trait, BDI or CDI. Although this was done to remove any pre-test group differences and to ensure that only healthy participants were included, removing these participants (n = 10) might have limited the variability of our sample and thus the power to detect a correlation.

Another questionnaire measure that was included in **Chapter 4** was the BIS/BAS scales (Carver & White, 1994). As discussed before (see General Introduction and section 1.4), this was done to examine some of the claims made by the triadic model, with regard to the neural basis of approach and avoidance behaviour. Although BIS and BAS sensitivity have previously been linked to amygdala and VS activation, respectively (Beaver, Lawrence, Passamonti, & Calder, 2008; Beaver et al., 2006; Reuter et al., 2004), we failed to find a significant correlation between Total BIS or Total BAS scores and activity in the ROIs for the 0-back or 2-back task separately, or for the whole task, in adolescents nor adults.

A final questionnaire, that was administered in adolescents only, was the Pubertal Development Scale (PDS; Petersen et al., 1988). Previous studies have shown that pubertal development and age have both independent and interactive influences on structural (Goddings et al., 2014) and functional brain development (for a review, see Blakemore, Burnett, & Dahl, 2010; Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012; Klapwijk et al., 2013; Moore et al., 2012). For instance, a recent study indicated that even when controlling for chronological age, pubertal development is

related to neural responses to emotional faces in the amygdala and lateral prefrontal cortex (Moore et al., 2012). Unfortunately, we could not find any correlations between scores on the PDS and neural correlates of the emotional n-back task. As discussed before (see section 1.4), the Pubertal Development Scale (PDS) has a few disadvantages and is not ideally suited to assess pubertal development. Studies aimed at identifying pubertal influences on brain development should therefore use more direct measures, such as salivary hormone levels.

CLINICAL IMPLICATIONS

Although all studies in this thesis report findings in healthy participants, our results also contribute to the understanding of psychopathology, especially mood disorders. Across all empirical studies (**Chapter 3-5**), we have consistently found effects with regard to happy faces. In **Chapter 3**, we have shown that early adolescence (12-14 years of age) is characterized by an increased sensitivity towards these positive stimuli, thus extending previous findings on reward sensitivity during adolescence (Richards, Plate, & Ernst, 2013). As hypothesized by dual-process theories and the triadic model of adolescent behaviour (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), happy faces were found to influence WM performance to a larger extent in adolescents than adults.

Although the neural mechanism underlying this effect were not clear based on our fMRI findings (**Chapter 4**), indicating the need for further examination, this developmental difference might bear implications for understanding the development of depression during adolescence. Previous studies have found biases towards negative stimuli in depressed adolescents (Ladouceur et al., 2005) as well as adults (Levens & Gotlib, 2010). In our behavioural study with the emotional n-back task (**Chapter 3**), the opposite effect was found in healthy samples, i.e. a bias towards positive stimuli, and this finding was more pronounced in adolescents compared to adults. Consequently, increased attention towards appetitive cues such as happy faces might reduce the risk of developing depression in healthy individuals. Indeed, previous studies have shown that the ability to update positive information in WM is related to better life satisfaction and affect balance (Pe, Koval, et al., 2013) in adults. An intriguing question is whether

this also applies to adolescents. If so, then our finding that happy faces impact WM to a larger extent in adolescents compared to adults would suggest that adolescence have a higher life satisfaction, better affect balance and lower risk for developing depression.

Nevertheless, adolescence is characterized by increased negative mood and emotional instability. Environmental influences and subsequent changes in the processing of affective information might provide an explanation for this apparent contradiction. Healthy adolescents are generally found to be more sensitive to positive stimuli, such as happy faces (**Chapter 3**). This bias towards appetitive cues is thought to increase risk-taking, as proposed by neurobiological theories (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), but it could also constitute a protective factor for depression. However, if adolescents are constantly confronted with negative events in their environment (e.g. social exclusion), this might eventually undo the positivity bias seen in healthy adults or lead to biases towards negative stimuli, increasing vulnerability to depression. Our findings with regard to happy faces in students reporting physical or sexual abuse corroborate these suspicions. Whereas healthy controls and students reporting other types of childhood stress showed a better WM performance for happy compared to neutral faces, this effect was absent in students with a history of childhood physical or sexual abuse. Childhood trauma thus seems to alter the processing of positive stimuli, which could offer an explanation for the increased incidence of depression in this sample (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001).

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

One of the main aims of this thesis was to study emotional WM and its neural correlates during adolescence. Even though the performance of adolescents on an emotional n-back task was compared to adults in **Chapter 3 and 4**, the absence of a younger age group limits interpretation with regard to theories of adolescent behaviour. The decision to not include children in these studies was due to a number of practical considerations. First of all, the emotional 2-back task is a challenging task, as was evident from performance measures in the youngest adolescents. Second, even

though adolescents participating in the fMRI study were well prepared for the scan session using the dummy scanner, a substantial amount (n = 10) of 12-16 year olds had to be excluded due to excessive head movement. To avoid a large proportion of exclusions, no younger children were included in the study. Future studies could address these limitations by using a different WM task that is suitable for younger age groups. For fMRI studies in developmental populations, it is advisable to use short scan runs and to limit the total scan time, in order to avoid excessive head movement.

Another limitation is related to the selection of emotional stimuli, i.e. angry, happy and neutral faces. It is unclear whether the effects reported with these stimuli are generalizable to other facial expressions, such as fearful or sad faces. Although angry and fearful faces are both threat-related, they have a different meaning for the viewer. While fearful faces indicate a possible threat in the environment, angry faces convey a direct threat to the viewer. A study by Davis et al. (2011) indicated that both faces affect memory differently, with angry faces being recalled more easily than fearful faces, even though these faces did not differ in valence or arousal. With regard to positively valenced faces, most studies use happy faces, while the effects of other positive expressions such as pride or joy are less clear. Given that all of these expressions communicate a different message, it would be interesting to examine whether they affect working memory – and other cognitive processes – similarly. Finally, even though neutral faces were used in our empirical studies to serve as a control condition or baseline, compared to faces conveying an emotional meaning, studies have shown that neutral faces or not always perceived as neutral. Instead, in healthy adults neutral faces are sometimes evaluated as negative (Lee, Kang, Park, Kim, & An, 2008). And this effect is exacerbated in clinical samples, such as anxious or depressed individuals (Leppanen, Milders, Bell, Terriere, & Hietanen, 2004; Yoon & Zinbarg, 2008). Therefore, we would recommended future research to include another control condition, for example scrambled or inverted faces.

An important factor that we did not examine in our empirical studies due to small sample sizes is the impact of gender on emotional WM performance and its neural correlates. In adults, gender-specific activation patterns have been found when performing an n-back WM task with negative mood induction (Koch et al., 2007). Whereas men increasingly activated prefrontal and superior parietal regions, this task

yielded stronger responses in amygdala and orbitofrontal cortex in women. This relative hyper-activation of emotional areas could offer an explanation for increased vulnerability to depression in women (Sloan & Kornstein, 2003). Gender differences in depression rates emerge during adolescence, with adolescent girls being twice as likely to develop depression compared to an equal gender ratio for prepubescent boys and girls (Nolen-Hoeksema & Girgus, 1994). Therefore, studying gender differences in the cortico-limbic circuitry underlying emotion processing and regulation will increase our understanding of adolescent-onset depression.

A complementary line of future research to gain more insight into the development and maintenance of adolescent depression is to compare healthy adolescents to depressed peers. In our developmental studies (**Chapter 3 and 4**), only healthy adolescents were included, in order to get an idea of the behavioural and neurological basis of emotional WM. However, the next step is to examine these processes in depressed adolescents. In adults, Levens and Gotlib (2010) have shown that compared to healthy controls, depressed individuals show maladaptive biases in the updating of positive and negative stimuli. An intriguing question is whether the same patterns can be found in adolescents.

FINAL CONCLUSION

The main aim of this thesis was to examine how irrelevant and relevant emotional stimuli are maintained in WM during adolescence, both on a behavioural as well as on a neurological level. Since there is no consensus on the neural correlates in adults, we first reviewed the adult literature about emotional influences on WM, but also on other cognitive control processes such as inhibition and task-switching. A meta-analysis on this data indicated several regions in the brain that seem to play a role in integrating emotion and cognitive control. These included areas in the prefrontal cortex and limbic system, as expected, but also a few clusters in the parietal and occipital cortex. We then used the findings from this meta-analysis to investigate emotional WM in adolescents. In a behavioural study, we found that happy faces impacted WM performance to a larger extent in adolescents than adults, and that performance of both groups was

influenced by the relevance of the emotional valence of our stimuli. If the valence was relevant for the task goal, WM performance improved for happy faces in both age groups, and if the emotional expression was irrelevant WM performance decreased in adolescents but not in adults. A subsequent fMRI study indicated differential activation patterns in adolescents and adults in several clusters identified in the meta-analysis. In general, adolescents showed increased activation in bilateral amygdala and decreased activation in a range of fronto-parietal regions, especially the right DLPFC and left IFG. In a final study, we wanted to examine how traumatic life events while growing up alter the way that emotions are maintained in WM later in life. We found that individuals who had experienced physical or sexual abuse during childhood or adolescence showed a deficit for processing positive stimuli, i.e. happy faces. This deficit could be an underlying mechanism explaining the increasing rates of psychopathology in individuals with a history of childhood trauma.

To conclude, our studies have been important in revealing developmental differences and the impact of stressful life events during childhood on emotional WM. However, future studies are needed to corroborate our results and extend our findings, for example to other cognitive control skills and emotional stimuli. Further research is also necessary to detect the exact role of the brain regions that were found in the meta-analysis and developmental fMRI study. And last but not least, it is important to expand the research on emotional WM in psychopathological disorders, such as depression, especially in developmental populations. This would allow us to gain more insight into the pathways leading to these disorders and eventually improve treatment.

"*To know what you know and what you do not know, that is true knowledge*"

Confucius

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NEDERLANDSTALIGE SAMENVATTING

Cognitie en emotie worden vaak voorgesteld als twee tegengestelden: hoofd versus hart, redeneren versus intuïtie, en denken versus voelen. Lange tijd heeft deze tegenstelling ook het psychologisch onderzoek beïnvloedt, waardoor ze apart bestudeerd werden. Maar om menselijk gedrag volledig te begrijpen is het uiteraard noodzakelijk om de interactie tussen beide processen te onderzoeken.

Het laatste decennium is de interesse in zulke emotie-cognitie interacties sterk toegenomen. Ontwikkelingen in het domein van cognitieve en affectieve neurowetenschappen hebben hier een belangrijke rol in gespeeld. In tegenstelling tot het courante idee dat cognities en emoties in de hersenen apart verwerkt worden, hebben studies aangetoond dat dit niet het geval is (J. R. Gray, 2004; Pessoa, 2008, 2009). Hersendelen die vroeger als 'cognitief' beschouwd werden, zoals de prefrontale cortex, blijken gevoelig voor emotionele informatie (Erk, Kleczar, & Walter, 2007; Goldstein et al., 2007; Perlstein, Elbert, & Stenger, 2002), en delen die traditioneel geassocieerd werden met emotie, zoals de amygdala, spelen een rol in cognitieve processen (Blair et al., 2007; Schaefer et al., 2006; Schaefer & Gray, 2007; Silvert et al., 2007). Het gevolg van deze bevindingen is dat onderzoek naar cognitieve processen niet enkel meer gebeurt in een neutrale context of met emotioneel neutrale informatie maar dat er ook wordt nagegaan hoe affectieve informatie cognitieve controle processen kan beïnvloeden.

Cognitieve control is een veelomvattende term voor een verscheidenheid aan mentale processen die nodig zijn om ons gedrag aan te passen aan huidige doelen. Miyake et al. (2000) hebben aangetoond dat cognitieve control kan onderverdeeld worden in drie gerelateerde maar te onderscheiden processen: 1) set shifting, d.i. de vaardigheid om tussen verschillende taken te wisselen, 2) inhibitie, d.i. het onderdrukken van een reactie, en 3) updating, dat verwijst naar het behouden en vernieuwen van informatie in het werkgeheugen. Emotie beïnvloedt elk van deze functies (Diaz et al., 2011; Dolcos & McCarthy, 2006; Dreisbach & Goschke, 2004; Egner, Etkin, Gale, & Hirsch, 2008), maar de laatste speelt een belangrijke rol bij

emotieregulatie (Joormann & D'Avanzato, 2010; Pe, Raes, & Kuppens, 2013). Het werkgeheugen is een systeem met een beperkte capaciteit die instaat voor het opslaan en manipuleren van informatie gedurende korte tijd, vóór deze informatie naar het lange termijn geheugen wordt doorverwezen (Baddeley, 2003). Omwille van de beperkte capaciteit, is het van cruciaal belang om te controleren welke informatie geactiveerd blijft in het werkgeheugen. In een emotionele context gaat dit dan zowel over het vermijden dat irrelevante affectieve informatie in het werkgeheugen geactiveerd wordt, maar evengoed over het efficiënt onthouden en vernieuwen van relevante emotionele informatie. Eerder onderzoek heeft aangetoond dat het efficiënt vernieuwen van affectieve stimuli in het werkgeheugen gerelateerd is aan subjectief welzijn (Pe, Koval, & Kuppens, 2013) en persoonlijkheidskenmerken zoals optimisme en pessimisme (Levens & Gotlib, 2012), en dat individuen die te kampen hebben met een depressie (Joormann & Gotlib, 2008; Levens & Gotlib, 2010; Linden, Jackson, Subramanian, Healy, & Linden, 2011) of angststoornis (Fales et al., 2008; Lavric, Rippon, & Gray, 2003; Shackman et al., 2006) hier vaak problemen mee hebben, bijvoorbeeld wat betreft het vermijden van irrelevante negatieve informatie.

In tegenstelling tot de toenemende interesse voor emotioneel werkgeheugen bij volwassenen, vooral in het kader van depressie-onderzoek, zijn er weinig studies die dit hebben onderzocht bij kinderen of adolescenten. Nochtans is dit een erg interessante periode voor zulk onderzoek, aangezien de adolescentie gekenmerkt wordt door unieke neuropsychologische veranderingen op het vlak van emotie en cognitie. Tijdens de adolescentie is er namelijk een onevenwicht in de ontwikkeling van hersenregio's die voor beide processen instaan. Op het cognitieve vlak is er een lineaire vooruitgang (Luna, 2009), waardoor jongeren in toenemende mate in staat zijn om te redeneren, te plannen en beslissingen te nemen. Deze vooruitgang is vooral te wijten aan de ontwikkeling van de prefrontale cortex, die instaat voor de controle van ons gedrag. Uit onderzoek blijkt echter dat jongeren hun cognitieve vaardigheden niet optimaal kunnen benutten wanneer ze zich in een emotionele context bevinden. Volgens verschillende neurobiologische theorieën (Ernst, Pine, & Hardin, 2006; Somerville & Casey, 2010; Steinberg, 2008) is dit te wijten aan 1) een verhoogde gevoeligheid voor emotionele informatie, wat blijkt uit verhoogde activatie in emotionele hersengebieden (amygdala en ventraal striatum), en 2) een nog niet voldoende ontwikkeld regulatiesysteem (in de

prefrontale cortex), waardoor ze onvoldoende in staat zijn om activatie in emotionele gebieden onder controle te houden (zie Figuur 1 in **hoofdstuk 1**).

Het algemene doel van deze verhandeling was om te onderzoeken hoe relevante en irrelevante emotionele informatie wordt opgenomen in het werkgeheugen van gezonde adolescenten in vergelijking met volwassenen, en dit zowel op gedragsmatig als op neurobiologische vlak. Hiervoor werd steeds gebruikt gemaakt van een werkgeheugentaak met emotionele stimuli, namelijk blije, boze en neutrale gezichten. Bovendien gingen we ook na hoe stresserende ervaringen tijdens de jeugd beïnvloeden hoe (irrelevante) emotionele informatie wordt opgenomen in het werkgeheugen. De belangrijkste bevindingen van deze studies worden hieronder besproken.

OVERZICHT VAN DE BELANGRIJKSTE BEVINDINGEN

1. Gedragsmatige resultaten

1.1 De invloed van (ir)relevante emotie op het werkgeheugen

Onderzoek naar de impact van emotionele stimuli op cognitieve controle duidt soms op een gedragsmatige verbetering tegenover neutrale stimuli (Kanske & Kotz, 2011; Levens & Phelps, 2008), terwijl anderen rapporteren dat emotionele stimuli een nadelige invloed uitoefenen op cognitieve controle vaardigheden (Blair et al., 2007; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos & McCarthy, 2006). Eén van de doelstellingen van deze thesis was om te onderzoeken in welke mate de relevantie van emotie voor de cognitieve controle taak hierin een rol speelt. Om dit na te gaan, lieten we een groep adolescenten en volwassenen een emotionele werkgeheugentaak uitvoeren. Onze bevindingen toonden duidelijk aan dat de relevantie van emotie voor de werkgeheugentaak de prestatie beïnvloedt, zowel bij adolescenten als bij volwassenen.

Indien aan deelnemers gevraagd werd om de gelaatsuitdrukking van het gezicht te onthouden (*emotietaak*), reageerden zowel adolescenten als volwassenen sneller op blije gezichten dan op boze of neutrale gezichten. Dit effect werd ook gevonden in

hoofdstuk 4, waarin deelnemers dezelfde taak uitvoerden in de hersenscanner. Bovendien komt dit overeen met de bevindingen van Levens en Gotlib (2010), die een gelijkaardige taak afnamen bij volwassenen. Zij suggereerden dat dit voordeel voor blije gezichten in het werkgeheugen een bias voor positieve informatie weergeeft. Een gelijkaardige bias voor positieve informatie bij volwassenen werd ook reeds gevonden in andere onderzoeksdomeinen, zoals aandacht (Joormann & Gotlib, 2007; Sanchez, Vazquez, Marker, LeMoult, & Joormann, 2013) en woordverwerking (Herbert, Kissler, Junghofer, Peyk, & Rockstroh, 2006; Kuchinke et al., 2005). Blije gezichten lijken de aandacht dus makkelijker te trekken dan andere gelaatsuitdrukkingen, tenminste bij gezonde deelnemers, en dit heeft ook een effect op het werkgeheugen.

In tegenstelling tot de eenduidige resultaten bij de emotietaak, waren de resultaten van de *gendertaak*, waarbij gevraagd werd om het geslacht te onthouden, minder rechtlijnig. In de gedragsmatige studie (**hoofdstuk 3**) reageerden adolescenten trager op blije gezichten, terwijl de prestatie van volwassenen niet beïnvloed werd door de emotionele gelaatsuitdrukking van het gezicht. In de fMRI studie (**hoofdstuk 4**) waren beide groepen trager bij het zien van boze gezichten. Deze uiteenlopende resultaten kunnen verklaard worden door methodologische verschillen tussen beide studies. Het aantal proefpersonen was bijvoorbeeld kleiner in de fMRI studie, waardoor er mogelijks te weinig power was om een effect te vinden. Bovendien was er ook een verschil in leeftijdscategorie. Terwijl adolescenten in de gedragsstudie tussen 12 en 14 jaar waren en volwassenen tussen 18 en 29 jaar, waren die leeftijdscategorieën in de fMRI studie respectievelijk 12 tot 16 en 25 tot 35 jaar. Tenslotte kan ook de testomgeving (rustig onderzoekslokaal vs. luidruchtige scanner) de prestatie beïnvloed hebben.

1.2 Individuele verschillen en emotioneel werkgeheugen

Overheen de verschillende studies (**hoofdstuk 3-5**) werd geen verband gevonden tussen individuele verschillen (gebaseerd op zelfrapportage vragenlijsten) en prestatiematen. Vragenlijsten die telkens afgenomen werden, waren de Beck Depressie Vragenlijst (BDI-II NL; Beck, Steer, Ball, & Ranieri, 1996; van der Does, 2002), de Depressievragenlijst voor kinderen (CDI; Kovacs, 1992; Timbremont, Braet, & Roelofs,

2008), en angstvragenlijsten, namelijk de Zelfbeoordelingsvragenlijst (ZBV of STAI; Spielberger, Gorsuch, & Lushene, 1970) en de Zelfbeoordelingsvragenlijst voor kinderen (ZBV-K of STAI-C; Bakker, van Wieringen, van der Ploeg, & Spielberger, 2004; Spielberger, 1973). Eerder onderzoek toonde aan dat individuele verschillen, zoals zelf-gerapporteerde angstdispositie en depressieve symptomen, gerelateerd zijn aan werkgeheugen voor emotionele stimuli (Joormann & Gotlib, 2008; Ladouceur et al., 2009; Levens & Gotlib, 2010, 2012; Pe, Raes, et al., 2013). Bijvoorbeeld, Ladouceur et al. (2009) rapporteerden dat hoog-angstige personen (8-30 jaar) trager zijn op een 2-back taak waarbij angstige gezichten als afleider gebruikt worden. Dit effect was ook groter bij jongere deelnemers (kinderen en adolescenten). In onze studies vonden we echter geen significante correlaties tussen toestandsangst en de prestatie om de emotionele werkgeheugentaak. Ook scores op de depressievragenlijst bleken niet gerelateerd aan die prestatie. Dit zou kunnen liggen aan de selectie van proefpersonen. In **hoofdstuk 3-5** werden deelnemers vooraf gescreend met de Adult Self Report (ASR; Achenbach & Rescorla, 2003) of de ouderversie van de Child Behaviour Checklist (CBCL; Achenbach & Rescorla, 2001). Deelnemers die klinisch scoorden op deze screening werden uitgesloten in **hoofdstuk 3 en 4**, aangezien deze studies betrekking hadden op gezonde deelnemers zonder psychopathologie. In **hoofdstuk 5** werden deelnemers met een klinische score op de ASR of CBCL niet uitgesloten, maar ook hier vonden we geen significante correlaties tussen scores op de ZBV of BDI enerzijds en reactietijden of accuraatheid op de experimentele taak anderzijds.

Een andere vragenlijst die werd afgenomen in de studies met adolescenten (**hoofdstuk 3 en 4**) is de Behavioural Inhibition/Behavioural Activation System scales (BIS/BAS scales; Carver & White, 1994). Deze vragenlijst is gebaseerd op de biopsychosociale persoonlijkheidstheorie van Gray (1970), die stelt dat individuele verschillen worden verklaard door de gevoeligheid voor straf (BIS) en voor beloning (BAS). De BIS/BAS schalen werden afgenomen in onze studies om na te gaan of verschillen in gevoeligheid voor beloning en straf een verklaring kunnen bieden voor onze bevindingen op de emotionele werkgeheugentaak. Er werden in beide studies (**hoofdstuk 3 en 4**) echter geen significante correlaties gevonden.

Een laatste maat van individuele verschillen die afgenomen werd in de fMRI studie (**hoofdstuk 4**), was de Pubertal Development Scale (PDS; Petersen, Crockett,

Richards, & Boxer, 1988). Ook al is leeftijd en puberale ontwikkeling sterk gerelateerd, er is nog steeds een grote variatie qua puberale fase binnen eenzelfde leeftijdscategorie. Om het effect van beide factoren te onderscheiden, werd daarom de PDS afgenomen bij adolescenten. Er werden echter geen significante correlaties gevonden tussen de score op de PDS vragenlijst en de prestatie op de werkgeheugentaak. Niettegenstaande dat de PDS een handig en snel meetinstrument is om te bepalen in welke fase van puberale ontwikkeling een individu zich bevindt, zijn correlaties met het oordeel van artsen toch tamelijk zwak, namelijk tussen .61 en .67 (Brooks-Gunn, Warren, Rosso, & Gargiulo, 1987). Dit zou dan ook kunnen verklaren waarom er geen correlatie gevonden werd.

1.3 Emotioneel werkgeheugen in een kwetsbare groep

Eerder onderzoek heeft aangetoond dat individuen die tijdens hun kindertijd of adolescentie stresserende gebeurtenissen ervaren een verhoogde kans hebben op het ontwikkelen van psychopathologie als volwassene (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001). Dit verhoogd risico zou mogelijks samenhangen met het effect van zulke ervaringen op de emotionele (Gibb, Schofield, & Coles, 2009; Maheu et al., 2010; Masten et al., 2008; Tottenham et al., 2010) en cognitieve ontwikkeling (De Bellis, Hooper, Spratt, & Woolley, 2009; Jovanovic et al., 2012; Majer, Nater, Lin, Capuron, & Reeves, 2010) en op de interactie tussen beide factoren (Mueller et al., 2012; Mueller et al., 2010). In **hoofdstuk 5** onderzochten we of stresserende ervaringen tijdens de jeugd een invloed hebben op de manier waarop emotionele informatie wordt opgeslaan in het werkgeheugen. Met behulp van een emotionele spatiale werkgeheugentaak vergeleken we studenten die tijdens hun jeugd fysiek of seksueel misbruik rapporteerden (misbruik groep) met studenten die andere stresserende ervaringen hadden meegemaakt tijdens hun jeugd, zoals het verlies van een ouder of getuige zijn van geweld (stress groep) en studenten die geen stresserende ervaringen tijdens de jeugd meldden (controle groep). De resultaten toonden aan dat vrouwen in de misbruik groep in de moeilijkste conditie (irrelevante) positieve stimuli minder goed hadden opgeslaan in het werkgeheugen, vergeleken met zowel de stress als de controle groep. Hierbij werd bovendien gecontroleerd voor scores op de depressie- en angstvragenlijsten. Deze bevindingen waren enigszins onverwacht. Aangezien trauma

tijdens de kindertijd een risicofactor is om later in het leven psychopathologische stoornissen te ontwikkelen, voornamelijk depressie- en angststoornissen (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001), en gebaseerd op onderzoek bij depressieve en angstige populaties waarin aangetoond werd dat deze groepen aandachts- en werkgeheugenbiases vertonen voor negatieve stimuli (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Gotlib & Joormann, 2010; Mathews & MacLeod, 2005; Peckham, McHugh, & Otto, 2010), hadden we verwacht een effect te vinden voor boze en niet blije gezichten. Omdat er erg weinig onderzoek is naar de verwerking van positieve stimuli in slachtoffers van misbruik is het onduidelijk hoe deze bevindingen verklaard kunnen worden. Een mogelijke verklaring is dat individuen die misbruikt werden positieve informatie zoals blije gezichten minder efficiënt encoderen in het werkgeheugen, waardoor het moeilijker is om deze informatie terug op te roepen. De bevinding dat emotionele effecten enkel aanwezig waren in de moeilijkste conditie zou een plafondeffect kunnen zijn. Een andere mogelijkheid is dat slachtoffers van misbruik hun aandacht net meer richten op de emotionele waarde van positieve stimuli, maar dat ze andere kenmerken van deze stimuli zoals de locatie minder goed opslaan in het werkgeheugen. Een recente studie waarbij gebruik gemaakt werd van de dot-probe taak met boze en blije gezichten (Fani et al., 2012) toonde namelijk aan dat volwassenen met misbruikervaringen tijdens de kindertijd hun aandacht meer richten naar blije gezichten. Aangezien biases naar positieve stimuli meestal als adaptief beschouwd worden (Joormann & Gotlib, 2007) en gerelateerd zijn aan emotioneel welzijn (Pe, Koval, et al., 2013), gaat deze bevinding tegen onze verwachtingen in. In de studie van Fani et al. (2012), was een bias naar blije gezichten echter geassocieerd met symptomen van post-traumatische stress stoornis (PTSD). Volgens deze onderzoekers zou excessieve aandacht voor positieve stimuli gerelateerd kunnen zijn aan het vermijden van bedreigende stimuli, waardoor extinctie niet plaatsvindt en PTSD in stand gehouden wordt. Deze interpretatie is uiteraard speculatief en er is meer onderzoek nodig om te onderzoek wat de exacte rol is van een bias voor positieve stimuli bij slachtoffers van misbruik.

2. Neurobiologische bevindingen

2.1 Emotie cognitie interacties bij volwassenen

Zoals blijkt uit de bespreking van de gedragsmatige bevindingen, hebben emotionele stimuli een invloed op het werkgeheugen, zowel bij adolescenten als bij volwassenen. Een vraag die vele onderzoekers intrigeert is welke regio's in de hersenen belangrijk zijn bij zulke emotie-cognitie interacties. Hoewel een aantal recente studies zich reeds over deze vraag gebogen heeft (Dolcos et al., 2008; Dolcos & McCarthy, 2006; Mohanty et al., 2005; Sagaspe, Schwartz, & Vuilleumier, 2011), is er geen consensus over de neurologische basis. Daarom hebben we in **hoofdstuk 2** onderzocht welke regio's consistent geactiveerd worden bij cognitieve controle taken binnen een emotionele context, met behulp van de Activation Likelihood Estimation (ALE) methode. In deze meta-analyse werden clusters gevonden in de prefrontale cortex (rechter dorsolaterale prefrontale cortex, bilaterale inferieure frontale gyrus, superieure/mediale frontale gyrus), de pariëtale cortex (inferieure pariëtale lob), en subcorticale regio's (amygdala, anterieure insula).

Een belangrijke bijdrage van deze studie is dat deze veel gedetailleerder weergeeft welke delen in de hersenen belangrijk zouden kunnen zijn voor de integratie van cognitieve controle processen en emotieverwerking. In de literatuur werden reeds een aantal theoretische modellen (o.a. Pessoa, 2008) voorgesteld, maar deze waren over het algemeen eerder vaag over de precieze anatomische locatie van belangrijke integratieregio's. Een andere bijdrage van de meta-analyse betreft de empirische evidentie voor de betrokkenheid van de pariëtale cortex, anterieure insula en zelfs de occipitale cortex bij emotie-cognitie interacties.

2.2 Neurologische bevindingen van de emotionele werkgeheugentaak bij adolescenten en volwassenen

In **hoofdstuk 4** werd nagegaan hoe de verschillende clusters uit de meta-analyse geactiveerd werden tijdens de emotionele werkgeheugen taak, bij adolescenten en volwassenen. Op basis van eerder onderzoek en neurobiologische theorieën die veronderstellen dat er tijdens de adolescentie een onevenwicht is tussen emotionele en cognitieve informatieverwerking (Ernst et al., 2006; Somerville & Casey, 2010;

Steinberg, 2008), verwachtten we verschillen te vinden tussen volwassenen en adolescenten in de (pre)frontale cortex en limbische regio's. De resultaten toonden aan dat adolescenten in vergelijking met volwassenen minder activiteit vertoonden in een aantal frontale clusters, zoals de inferieure frontale gyrus (IFG), dorsolaterale prefrontale cortex (DLPFC) en superieure/mediale frontale gyrus (SFG/MFG). Bovendien was activiteit in deze delen positief gecorreleerde met de prestatie op de werkgeheugentaak in volwassenen maar niet in adolescenten. Deze bevinding suggereert dat adolescenten in minder mate op deze frontale regio's steunen om de taak uit te voeren. Dit komt overeen met het idee dat activatie verschuift van een diffuus naar focaal patroon doorheen de ontwikkeling (Bunge & Wright, 2007; Crone, 2009; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Klingberg, Forssberg, & Westerberg, 2002). In vergelijking met adolescenten activeerden volwassenen ook andere clusters in sterkere mate (bijvoorbeeld de fusiforme gyrus en inferieure pariëtale lob). Activiteit in deze regio's hield eveneens verband met de prestatie op de taak, zoals bleek uit de positieve correlatie met accuraatheid. Deze bevindingen tonen aan dat het netwerk dat bij volwassenen instaat voor werkgeheugen gedurende de adolescentie nog steeds immatuur is.

Bovendien werd de activiteit in twee frontale regio's beïnvloed door de gelaatsuitdrukking van de gezichten bij volwassenen, maar niet bij adolescenten. Zowel de rechter DLPFC als de linker IFG werd bij volwassenen meer geactiveerd tijdens het tonen van boze versus blije of neutrale gezichten, terwijl activiteit in deze regio's niet beïnvloed werd door de emotionele stimuli in de groep van adolescenten. Verhoogde activiteit in de rechter DLPFC zou mogelijks te wijten zijn aan het behoud van aandachtscontrole wanneer men geconfronteerd wordt met biologisch relevante, emotionele informatie zoals boze gezichten (Banich et al., 2009; Blasi et al., 2007; Dolcos et al., 2008). De linker IFG zou een rol kunnen spelen in het verminderen van de effecten van emotionele stimuli op hogere-orde cognitieve processen door middel van het onderdrukken van activiteit in affectieve regio's, zoals de amygdala (Anticevic, Repovs, & Barch, 2010; Dolcos & McCarthy, 2006; Mincic, 2010).

Verschillen tussen beide groepen werden trouwens ook gevonden in de amygdala. Adolescenten activeerden de linker amygdala in sterkere mate wanneer ze geconfronteerd werden met boze vs. blije/neutrale gezichten in de gendertaak, wat

mogelijks wijst op een hogere afleiding door deze emotionele informatie (Anticevic et al., 2010; Dolcos et al., 2008; Dolcos & McCarthy, 2006). In de rechter amygdala had enkel cognitieve belasting een impact op de activatie, met meer activiteit voor de 2-back in vergelijking met de 0-back conditie bij adolescenten dan volwassenen. Dit zou kunnen liggen aan de nog niet volledig ontwikkelde top-down controle van amygdala activatie bij adolescenten (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008).

2.3 Implicaties voor neurobiologische theorieën van de adolescentie

Over het algemeen bevestigen onze bevindingen de hypotheses van neurobiologische theorieën van de adolescentie (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), namelijk prefrontale hypo-activiteit en limbische hyperactiviteit. Zoals in de vorige paragraaf reeds vermeld werd, vertoonden volwassenen vergeleken met adolescenten een hogere activiteit in verschillende prefrontale regio's. De verschillen tussen beide groepen waren echter niet beperkt tot de prefrontale cortex (PFC). Volwassenen activeerden ook andere regio's in sterkere mate dan adolescenten, met name de inferieure pariëtale lob, fusiforme gyrus, insula, en precuneus. Bovendien was de neurale activiteit in de rechter DLPFC en linker IFG afhankelijk van de emotionele gelaatsuitdrukking van de gezichten bij volwassenen, maar niet bij adolescenten. Dit wijst mogelijk op onderontwikkelde prefrontale top-down regulatie van hyperactieve subcorticale regio's, zoals Hare et al. (2008) suggereren. In die studie voerden kinderen, adolescenten en volwassenen een emotionele go/no-go taak uit in de fMRI scanner. De resultaten toonden aan dat amygdala activiteit hoger was bij adolescenten dan bij volwassenen en kinderen, en dat habituatie van deze activiteit gerelateerd was aan functionele connectiviteit tussen de ventrale PFC en de amygdala. In onze studie was er eveneens een cluster in de ventrale PFC, namelijk in de linker IFG, die meer activiteit vertoonde wanneer boze gezichten getoond werden in vergelijking met neutrale gezichten, maar dit was enkel het geval voor volwassenen en niet voor adolescenten. De linker IFG speelt dus mogelijk een rol bij het beperken van de impact van emotionele stimuli op de werkgeheugentaak.

De bevindingen in de amygdala waren volgens de verwachtingen van neurobiologische theorieën van de adolescentie (Ernst et al., 2006; Somerville & Casey,

2010; Steinberg, 2008), met over het algemeen meer activiteit bij adolescenten dan bij volwassenen. We hadden echter ook activatieverschillen verwacht in het ventrale striatum (VS) voor blije versus neutrale gezicht in beide groepen, maar in sterkere mate bij adolescenten. Dit zou overeenkomen met het idee dat blije gezichten een soort beloning voorstellen (Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009; Spreckelmeyer et al., 2009), vooral voor adolescenten die geacht worden erg gevoelig te zijn voor zulke sociale signalen(Guyer, Choate, Pine, & Nelson, 2012; Jones et al., 2011; Somerville et al., 2013). In tegenstelling tot onze verwachtingen werden echter geen emotionele of groepsverschillen gevonden in het VS, wat er mogelijks op wijst dat betere prestatie voor blije gezichten niet te wijten is aan de belonende waarde van deze stimuli. Eerder onderzoek is niet eenduidig wat VS activatie voor blije gezichten betreft. Slechts één studie rapporteerde hogere VS activatie voor blije in vergelijking met neutrale gezichten in de context van een go/no-go task (Somerville, Hare, & Casey, 2011). Jammer genoeg includeerden Hare et al. (2008) het VS niet als region-of-interest (ROI) in hun studie. Er zijn dus meer studies nodig die de betrokkenheid van het VS voor de verwerking van blije gezichten bij adolescenten onderzoeken, bijvoorbeeld door de effecten van beloning en blije gezichten op VS activiteit rechtstreeks met elkaar te vergelijken in eenzelfde groep adolescenten.

2.4 Verband tussen individuele verschillen en neurale activatie tijdens de emotionele werkgeheugentaak

In tegenstelling tot onze verwachtingen, vonden we geen significante correlaties tussen neurale activatie in onze ROIs en verschillende vragenlijsten die peilden naar individuele verschillen, zoals angstdispositie en depressieve symptomen. Dit komt niet overeen met eerder onderzoek dat wel een relatie vond tussen angstniveau's en amgydala activatie voor negatieve – vooral angstige – gezichten, zowel bij gezonde adolescenten (Hare et al., 2008; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004) als volwassenen (Etkin et al., 2004), maar ook wanneer patiënten met een angststoornis vergeleken werden met gezonde controles (Evans et al., 2008; McClure et al., 2007; Monk, Telzer, et al., 2008; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Thomas et al., 2001). Onderzoek bij jongeren en volwassenen met een bepaalde kwetsbaarheid voor het ontwikkelen van een depressie duidt ook op abnormale

amygdala activatie in vergelijking met gezonde controles (Drevets, Price, & Furey, 2008; Monk, Klein, et al., 2008; Roberson-Nay et al., 2006; Surguladze et al., 2005; Thomas et al., 2001), hoewel de richting van dit effect niet zo eenduidig is als bij angstige individuen. Naast veranderingen in amygdala functioneren, werden bij depressieve patiënten ook reeds afwijkende reacties in het VS vastgesteld, vooral met betrekking tot de verwerking van blije gezichten (Epstein et al., 2006; Monk, Klein, et al., 2008). Op basis van deze bevindingen namen we aan dat er een significante correlatie zou zijn tussen amygdala en VS activatie enerzijds en angstdispositie of depressieve symptomen anderzijds. Zoals reeds vermeld werd in paragraaf 1.2 zou het ontbreken van zulke correlatie te wijten kunnen zijn aan de uitsluiting van deelnemers die klinisch scoorden op de ASR, CBCL, STAI(C), BDI of CDI. Ook al werd dit gedaan om vooraf bestaande groepsverschillen weg te werken en om ervoor te zorgen dat enkel gezonde individuen deelnamen, kan het zijn dat het verwijderen van deze deelnemers (n = 10) de variabiliteit van de sample beperkt heeft en dus ook de power om een correlatie te detecteren.

Een andere vragenlijst die werd afgenomen in de studie in **hoofdstuk 4** was de BIS/BAS scales (Carver & White, 1994). Hoewel BIS en BAS gevoeligheid in eerder onderzoek gelinkt werd aan respectievelijk amygdala en VS activatie (Beaver, Lawrence, Passamonti, & Calder, 2008; Beaver et al., 2006; Reuter et al., 2004), vonden wij noch bij adolescenten noch bij volwassenen significante correlaties tussen de Totale BIS of BAS score enerzijds en activiteit in de ROIs tijdens de 0-back, 2-back of beide taken samen anderzijds.

Een laatste vragenlijst die werd afgenomen bij adolescenten is de Pubertal Development Scale (PDS; Petersen et al., 1988). Eerdere studies hebben reeds aangetoond dat puberale ontwikkeling en leeftijd zowel gemeenschappelijke als aparte effecten hebben op structurele (Goddings et al., 2014) en functionele hersenontwikkeling (for a review, see Blakemore, Burnett, & Dahl, 2010; Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012; Klapwijk et al., 2013; Moore et al., 2012). Bijvoorbeeld, uit een recente studie bleek dat puberale ontwikkeling, zelfs als er gecontroleerd werd voor leeftijd, gerelateerd was aan de neurale activatie voor emotionele gezichten in de amygdala en laterale PFC (Moore et al., 2012). Wij konden echter geen verband aantonen tussen PDS scores en neurale activatie tijdens de

emotionele werkgeheugentaak. Zoals eerder aangehaald, (zie paragraaf 1.2) heeft de Pubertal Development Scale (PDS) een aantal nadelen en is het niet de ideale maat van puberale ontwikkeling. Studies die de invloed van puberteit op hersenontwikkeling willen onderzoeken, zouden daarom beter gebruik maken van andere, meer directe meetingen, zoals hormoonniveau's in het speeksel.

KLINISCHE IMPLICATIES

De resultaten van onze studies kunnen bijdragen aan het begrijpen van stemmingsstoornissen, ook al waren alle deelnemers gezonde vrijwilligers. Doorheen de verschillende empirische studies werd consistent een effect gevonden voor blije gezichten. In **hoofdstuk 3** toonden we aan dat de vroege adolescentie (12-14 jaar) wordt gekenmerkt door een verhoogde gevoeligheid voor positieve stimuli, in lijn met eerder onderzoek dat een hypersensitiviteit voor beloning rapporteerde (Richards 2013). Zoals verwacht op basis van neurobiologische theorieën (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008) beïnvloedden blije gezichten de werkgeheugenprestatie in sterkere mate bij adolescenten dan bij volwassenen. Dit verschil tussen beide leeftijdsgroepen heeft mogelijks implicaties voor het inzicht in depressie tijdens de adolescentie. Eerdere studies hebben biases gevonden naar negatieve stimuli in depressieve adolescenten (Ladouceur et al., 2005) en volwassenen (Levens & Gotlib, 2010). In onze gedragsstudie met de emotionele werkgeheugentaak (**hoofdstuk 3**), werd het omgekeerde effect gevonden in gezonde deelnemers, namelijk een bias voor positieve stimuli, en dit effect was sterker bij adolescenten dan bij volwassenen. Verhoogde aandacht voor positieve signalen zoals blije gezichten zou dus het risico op het ontwikkelen van depressie kunnen reduceren. Eerder onderzoek heeft inderdaad aangetoond dat het toelaten van positieve informatie in het werkgeheugen gerelateerd is aan een beter welbevinden en emotioneel evenwicht (Pe, Koval, et al., 2013) in volwassenen. Een vraag die zich dan stelt, is of dit hetzelfde is bij adolescenten. Indien wel, dan zou men op basis van onze bevindingen moeten besluiten dat adolescenten een hoger welzijn, betere emotioneel evenwicht en minder kans op

depressie hebben dan volwassenen. Nochtans wordt de adolescentie gekenmerkt door een negatieve gemoedstoestand en emotionele instabiliteit. Een mogelijke verklaring voor deze schijnbare tegenstelling zijn invloeden vanuit de omgeving die de manier waarop affectieve informatie verwerkt wordt, veranderen. Gezonde adolescenten zijn over het algemeen gevoeliger voor positieve stimuli (**hoofdstuk 3**). Neurobiologische theorieën gaan ervan uit dat deze bias gelinkt is aan risicovol gedrag (Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008), maar het zou evengoed een beschermende factor kunnen zijn voor het ontwikkelen van depressie. Het zou kunnen dat deze positieve bias verdwijnt als adolescenten erg vaak geconfronteerd worden met negatieve ervaringen (vb. sociale uitsluiting), en dit zou zelfs kunnen leiden tot een bias voor negatieve stimuli, waardoor de kans op depressie stijgt. Onze bevindingen bij studenten die tijdens hun jeugd fysiek of sexueel misbruik melden, lijken deze vermoedens te bevestigen. Hoewel gezonde controles en studenten met andere soorten stress tijdens hun jeugd een betere werkgeheugenprestatie hadden voor blije gezichten, was dit effect niet aanwezig bij studenten die fysiek of sexueel misbruik tijdens hun jeugd rapporteerden. Zulk trauma tijdens de kindertijd of adolescentie lijkt dus een invloed te hebben op de manier waarop positieve stimuli verwerkt worden, wat mogelijks kan verklaren waarom depressie vaker voorkomt in deze groep (Coffino, 2009; Green et al., 2010; MacMillan et al., 2001).

CONCLUSIE

Het doel van deze thesis was om te onderzoeken hoe (ir)relevante emotionele stimuli opgeslaan worden in het werkgeheugen tijdens de adolescentie, zowel op gedrags- als op neurobiologisch vlak. Zelfs in de volwassenliteratuur is er echter geen consensus over de neurologische basis van zulke emotie-cognitie interacties. Daarom hebben we deze studies eerst grondig bekeken en met behulp van een meta-analytische techniek onderzocht welke regio's in de hersenen belangrijk zijn bij de integratie van emotionele en cognitieve processen. De resultaten wezen op verschillende clusters in de prefrontale cortex en het limbisch systeem, zoals verwacht, maar ook clusters in de

pariëtale en occipitale cortex bleken een rol te spelen. De bevindingen van deze meta-analyse werden vervolgens gebruikt om emotioneel werkgeheugen bij adolescenten te onderzoeken. In een gedragsstudie vonden we dat blije gezichten het werkgheugen in sterkere mate beïnvloedden bij adolescenten dan bij volwassenen, en dat de prestatie van beide groepen afhankelijk was van de relevantie van de emotionele waarde van stimuli. Indien de emotie relevant was voor de taak, verbeterde de werkgeheugenprestatie voor blije gezichten in beide groepen, en indien de emotie niet relevant was, had dit enkel bij adolescenten een negatief effect op de werkgeheugenprestatie voor blije gezichten. Uit de fMRI studie bleek dat adolescenten en volwassenen ook andere activatiepatronen vertoonden in de hersenen tijdens het uitvoeren van de emotionele werkgeheugentaak. Over het algemeen was er bij adolescenten een verhoogde activiteit in de bilaterale amygdala, terwijl er minder activiteit was in een aantal fronto-pariëtale regio's, voornamelijk in de rechter DLPFC en linker IFG. In een laatste studie wilden we onderzoeken hoe traumatische ervaringen tijdens de jeugd beïnvloeden op welke manier men als volwassene emotionele informatie opslaat in het werkgeheugen. We vonden dat individuen die fysiek of sexueel misbruik hadden ervaren tijdens hun jeugd een verminderde prestatie toonden voor het verwerken van blije gezichten. Dit zou deels kunnen verklaren waarom individuen met een traumatische jeugd meer kans maken op het ontwikkelen van psychopathologie later in het leven.

Samengevat hebben onze studies belangrijke verschillen tussen volwassenen en adolescenten blootgelegd met betrekking tot hoe emotionele informatie opgeslaan wordt in het werkgeheugen. Bovendien hebben we ook aangetoond dat stresserende ervaringen tijdens de jeugd hierop een impact hebben. Er is echter nog meer onderzoek nodig om onze resultaten te bevestigen en uit te breiden, bijvoorbeeld naar andere cognitieve controle vaardigheden en emotionele stimuli. Bovendien is het belangrijk om te bepalen wat de exacte rol is van de hersenregio's die gevonden werden in de meta-analyse en de fMRI studie. En tenslotte is het ook belangrijk om onderzoek naar emotioneel werkgeheugen uit te breiden naar adolescenten die psychopathologie, bijvoorbeeld een depressie, ontwikkelen. Dit zou ons toelaten om beter te begrijpen hoe een depressie tijdens de adolescentie tot stand komt en zou op termijn kunnen leiden tot een betere behandeling.

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% Data Storage Fact Sheet
% Name/identifier study: "Probing emotional influences on cognitive control: an ALE meta-analysis of cognition emotion interactions" (Chapter 2)
% Author: Cromheeke Sofie
% Date: 10/03/2015

1. Contact details

1a. Main researcher

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2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:

- doctoral thesis Sofie Cromheeke (Chapter 2)
- Cromheeke, S., & Mueller, S. C. (2014). Probing emotional influences on cognitive control: an ALE meta-analysis of cognition emotion interactions. Brain Structure & Function, 219(3), 995-1008. doi: 10.1007/s00429-013-0549-z

* Which datasets in that publication does this sheet apply to?: entire dataset

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? [X] YES / [ ] NO

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- [X] all members of UGent
- [X] other (specify): everyone who has access to the papers that the meta-analysis is based on

3b. Other files

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- [x] file(s) describing the transition from raw data to reported results. Specify: see methodology in the thesis chapter
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containing all foci that were extracted from the papers referred to in the meta-analysis
- [x] file(s) containing analyses. Specify: results of the .xls files analyzed with GingerAle
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% Data Storage Fact Sheet
% Name/identifier study: "The power of a smile: stronger working memory effects for happy faces in adolescents compared to adults" (Chapter 3)
% Author: Cromheeke Sofie
% Date: 10/03/2015
1. Contact details
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2. Information about the datasets to which this sheet applies
==========
* Reference of the publication in which the datasets are reported:

- doctoral thesis Sofie Cromheeke (Chapter 3)
- Cromheeke, S., & Mueller, S.C. (in press). The power of a smile: stronger working memory effects for happy faces in adolescents compared to adults, Cognition & Emotion, doi: 10.1017/S0033291705005891
* Which datasets in that publication does this sheet apply to?: entire dataset
3. Information about the files that have been stored
==========
3a. Raw data
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* On which platform are the raw data stored?
- [X] researcher PC
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* Who has direct access to the raw data (i.e., without intervention of another person)?
- [X] main researcher
- [X] responsible ZAP
- [ ] all members of the research group
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3b. Other files
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* Which other files have been stored?
- [x] file(s) describing the transition from raw data to reported results. Specify: see methodology in Chapter 3
- [x] file(s) containing processed data. Specify: SPSS (.sav) and excel files (.xlsx)
- [X] file(s) containing analyses. Specify: SPSS outputs (.spv)
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- [ ] a file specifying legal and ethical provisions. Specify:
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- [ ] other files. Specify: ...
* On which platform are these other files stored?
- [x] individual PC
- [ ] research group file server
- [X] other: external hard drive of responsible ZAP
* Who has direct access to these other files (i.e., without intervention of another person)?
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% Data Storage Fact Sheet
% Name/identifier study: "Neural correlates of working memory for (ir)relevant emotional stimuli: a comparison between adolescents and adults" (Chapter 4)
% Author: Cromheeke Sofie
% Date: 10/03/2015

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2. Information about the datasets to which this sheet applies

==========

* Reference of the publication in which the datasets are reported: doctoral thesis Sofie Cromheeke
* Which datasets in that publication does this sheet apply to?: entire dataset

3. Information about the files that have been stored

==========

3a. Raw data

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* Have the raw data been stored by the main researcher? [X] YES / [ ] NO

If NO, please justify:

* On which platform are the raw data stored?
- [x] researcher PC: behavioural data and questionnaires
- [ ] research group file server
- [x] other (specify): fMRI data is stored on cd-roms, on an external hard drive of the responsible ZAP and on the server of the responsible ZAP

* Who has direct access to the raw data (i.e., without intervention of another person)
?
- [X] main researcher
- [X] responsible ZAP
- [ ] all members of the research group
- [ ] all members of UGent
- [ ] other (specify):

3b. Other files

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* Which other files have been stored?
- [x] file(s) describing the transition from raw data to reported results. Specify: see methodology in Chapter 4
- [X] file(s) containing processed data. Specify: stored on server of responsible ZAP
- [ ] file(s) containing analyses. Specify:
- [x] files(s) containing information about informed consent. Specify: all informed consents have been stored
- [ ] a file specifying legal and ethical provisions. Specify:

- [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
- [ ] other files. Specify: ...
* On which platform are these other files stored?
- [X] individual PC
- [ ] research group file server
- [X] other: server of the responsible ZAP
* Who has direct access to these other files (i.e., without intervention of another person)?
- [x] main researcher
- [x] responsible ZAP
- [ ] all members of the research group
- [ ] all members of UGent
- [ ] other (specify): ...

4. Reproduction

* Have the results been reproduced independently?: [ ] YES / [x] NO
* If yes, by whom (add if multiple):
- name:
- address:
- affiliation:
- e-mail:

% Data Storage Fact Sheet
% Name/identifier study: "Childhood abuse impacts working memory for positive emotion in female university students" (Chapter 5)
% Author: Cromheeke Sofie
% Date: 10/03/2015

1. Contact details

==========

1a. Main researcher

- name: Cromheeke Sofie
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Sofie.Cromheeke@UGent.be

1b. Responsible Staff Member (ZAP)

- name: Sven Mueller
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Sven.Mueller@UGent.be

2. Information about the datasets to which this sheet applies

==========

* Reference of the publication in which the datasets are reported:

- doctoral thesis Sofie Cromheeke (Chapter 5)
- Cromheeke, S., Herpoel, L. & Mueller, S.C. (2014). Childhood abuse impacts working memory for positive emotion in female university students, Child Maltreatment, 19(1), 38-48. doi: 10.1177/1077559513511522

* Which datasets in that publication does this sheet apply to?: entire dataset

3. Information about the files that have been stored

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3a. Raw data

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* Have the raw data been stored by the main researcher? [X] YES / [ ] NO

If NO, please justify:

* On which platform are the raw data stored?
- [x] researcher PC
- [ ] research group file server
- [x] other (specify): external hard drive of the responsible ZAP

* Who has direct access to the raw data (i.e., without intervention of another person)
?
- [x] main researcher
- [x] responsible ZAP
- [ ] all members of the research group
- [ ] all members of UGent
- [ ] other (specify):

3b. Other files

---

* Which other files have been stored?
- [x] file(s) describing the transition from raw data to reported results. Specify: see methodology chapter 5
- [x] file(s) containing processed data. Specify: SPSS files (.sav)
- [ ] file(s) containing analyses. Specify:
- [x] files(s) containing information about informed consent.

Specify: all informed consents have been stored
- [ ] a file specifying legal and ethical provisions. Specify:
- [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
- [ ] other files. Specify: ...
* On which platform are these other files stored?
- [x] individual PC
- [ ] research group file server
- [x] other: external hard drive of the responsible ZAP
* Who has direct access to these other files (i.e., without intervention of another person)?
- [x] main researcher
- [x] responsible ZAP
- [ ] all members of the research group
- [ ] all members of UGent
- [ ] other (specify): ...

4. Reproduction
==========
* Have the results been reproduced independently?: [ ] YES / [x] NO
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- name:
- address:
- affiliation:
- e-mail: